Pain Management, Lifestyle, and Dietary Choices by Australians with Fibromyalgia

By

Ms Cara Brown

Bachelor of Exercise Science (Clinical Practice)

Institute for Health and Sport (IHES)

Victoria University

A thesis submitted in fulfillment of the requirement for the degree of

Master of Applied Research

November 13th, 2021

Abstract

Background:

Fibromyalgia is a disease which is associated with widespread pain. Individuals with fibromyalgia self-report varied effectiveness for medications that target pain and lifestyle choices, physical activity and diet. However, there is no available data on the choices made by Australians with fibromyalgia. This study aimed to investigate pharmacotherapies for pain management, and lifestyle habits, physical activity and dietary choices used by Australians to manage their fibromyalgia symptoms.

Methods:

An observational, cross-sectional study comprising an online questionnaire (Qualtrics) was conducted in Australia from August 2020 to September 2020. A link to the online questionnaire was distributed via social media forums and a local pain clinic. Participants completed screening questions to assess eligibility to undertake the questionnaire. Inclusion criteria were diagnosis of fibromyalgia, residing in Australia, and over 18 years old. Subsequent questions gathered information about participant demographic, fibromyalgia symptoms, medication use and satisfaction, and exercise and dietary habits. A total of n = 185 participants consented and started the questionnaire. A small proportion of participants did not meet the inclusion criteria (did not have fibromyalgia, n = 4; did not live in Australia, n = 13), leaving a total of n = 162 included for analysis. As participants progressed through the questionnaire there were sequential dropouts, with n = 129 respondents completing the final question regarding incidental exercise. For the purposes of maximising the sample size for each question, all complete responses are included regardless of whether a respondent completed the full questionnaire. Ethical approval was obtained by the Victoria University Human Research Ethics Committee (HRE20-095).

Results:

Females comprised almost all of respondents initiating the questionnaire (female, n = 154; male, n = 6; other, n = 2), which decreased to 129 participants completing the survey. The age categories selected by respondents were: 18-24 years, 8%; 25-34 years, 17%; 35-44 years, 21%; 45-54 years, 31%; 55-64 years, 15%; 65-74 years, 7%; and 75+ years, 1%. Respondents reported experiencing pain for 7 days a week (67%), 5-6 days a week (19%), or 3 days a week or less (13%). Other significant symptom characteristics reported by this cohort were depression (74%), suicidal thoughts (39%), and thoughts of self-harm (32%). Respondents reported medications prescribed for symptoms of pain: paracetamol (66%), amitriptyline (59%), duloxetine (39%), pregabalin (31%), and tramadol (30%). The average number of pain medications prescribed was 3.3 (standard deviation, 2.1) per respondent. The magnitude of self-reported pain after taking the prescribed medications were no pain (3%), low level mild pain (9%), moderate pain (59%), distressing pain (29%), or extreme pain (1%). All

respondents reported the use non-prescribed therapies with an average of 3.5 (SD 2.9) per respondent, which included magnesium (73%), vitamin D (59%), vitamin B (50%), probiotics (49%), cannabidiol (19%) and, cannabis sativa (16%). Pain rating reported following cannabis plant or cannabidiol use was no pain (14%), low level pain (27%), moderate pain (18%), distracting pain (18%), or distressing pain (5%). Respondents reported whether they met or exceeded the dietary guidelines for each food group: vegetables, 21.8% ate five serves or more per day; fruit, 29.3% ate 2 serves or more per day; grains and cereals, 2.3% ate six serves or more per day; lean meats and alternatives, 78.2% ate two serves or more per day; dairy and alternatives, 52.6% ate two serves or more per day; and discretionary items, 82% ate two serves or less per day. Respondents reported the dietary fats regularly consumed in the diet: extra virgin olive oil (79%), animal butter (61%), coconut oil (36%), nut butter (21%), canola oil (21%), and margarine (21%). Diets reported to be trialled by participants were low sugar (81%), no alcohol (75%), gluten free (64%), reduced red meat (58%), low fat (53%), vegetarian (41%), whole foods (38%), and paleo (22%). Regular exercise was reported by 81% of respondents, with the preferred exercise being short walks (70%). Respondents reported their mean exercise intensity 2.8 (1-10 numeric score rating, NRS), and the mean exercise duration reported was 15-30 minutes (55%). Incidental exercise for ten minutes or longer for 3 or more times each week was reported by 37% of respondents.

Conclusion:

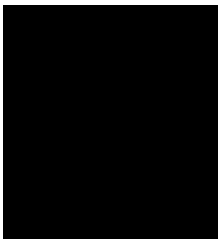
Those diagnosed with fibromyalgia in Australia are commonly prescribed more than three pain medication for the management of their symptoms. Despite the high use of prescribed and non-prescribed therapies, respondents reported regular and high levels of pain and poor mental health. More research is needed to understand the therapeutic value of prescribed and non-prescribed pharmacotherapy combinations for the management of fibromyalgia signs and symptoms in Australians with the condition. Additionally, responses to exercise and diet questions suggest Australians with fibromyalgia report poor adherence to Australian guideline recommendations for exercise and diet, with a small number of respondents reporting to consume adequate intake of all food groups and many trialling multiple diets for symptom management, alongside and low exercise volume and intensity and, a lack of resistance exercise. These lifestyle factors may contribute to fibromyalgia pain and other symptoms and may increase the use of pharmacotherapies and risk of developing comorbidities. To reduce the overall burden of the disease more research into physical activity, in particular resistance exercise at moderate intensities and, certain dietary modifications and the associated reduction in pain symptoms for Australians with fibromyalgia is required.

Keywords: paracetamol, cannabinoids, cannabis sativa, combination therapy, nutrition, physical activity, exercise therapy, suicidal ideation,

Master of Applied Research "I, Cara Brown, declare that the Master of Applied Research thesis entitled "Pain Management, Lifestyle, and Dietary Choices by Australians with Fibromyalgia" is no more than 50,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work".

"I have conducted my research in alignment with the Australian Code for the Responsible Conduct of Research and Victoria University's Higher Degree by Research Policy and Procedures".

"All research procedures reported in the thesis were approved by the Victoria University Human Research Ethics Committee, application ID: HRE20-095."

Signature  Date 13th November 2021

Dedication

This thesis is dedicated to those suffering from fibromyalgia who are seeking help and relief from pain. I also dedicate this thesis to my loving husband Tom, my family Chris, Janie, Daniel, Michael, and Rosie, Stephen and Catherine, and friends Karen, Christina and Pauline who have supported me through this phase of my life. A special mention of Ms Carmelina Monea for ongoing friendship and support during my studies.

Acknowledgment

I wish to express my deepest gratitude for the support and guidance, throughout my master's degree and for the contributions and edits to this thesis provided by my supervisors, Professor Andrew McAinch, and Dr André Nelson. The Victoria University staff of the Research Training, Quality and Integrity Office are also owed an acknowledgement for their support and guidance throughout the degree. A special thanks to Associate Professor Deborah Zion, Chair of the Human Research Ethics Committee, for her ethical guidance, and to Ms Karen Ines for her proof-reading services.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ACR	American College of Rheumatology Criteria
AEA	Anandamide
AMT	Amitriptyline
AWMF	Scientific Medical Societies in Germany
CB	Cannabinoid receptor
CBD	Cannabidiol
CBT	Cognitive Behavioural Therapy
CED	Clinical Endocannabinoid Deficiency
CFGC	Canadian Pain Society
CI	Confidence Interval
CoQ10	Co-enzyme Q10
COX	Cyclooxygenase 1, 2
DLX	Duloxetine
ECS	Endocannabinoid System
ES	Effect Size
EULAR	European League Against Rheumatism
EVOO	Extra virgin olive oil
FDA	Food and Drug Administration
FIQR	Fibromyalgia Impact Questionnaire (revised)
FODMAPs	Fermentable oligo-, di- and monosaccharides and polyols
GBP	Gabapentin
HAS	Hospital Anxiety Score
MLN	Milnacipran

MSM	Methyl-sulfonyl-methane
MU	μ-Opioid receptor
NRS	Numerical Rating Score
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
N-3	Omega 3 fatty acid
N-6	Omega 6 fatty acid
OA	Osteoarthritis
PDS	Polysymptomatic Distress Scale
PEA	Palmitoylethanolamide
PGB	Pregabalin
PPARα	Nuclear Peroxisome Proliferator-Activated Receptor-alpha
RPE	Borg Rating of Perceived Exertion Scale
SD	Standard Deviation
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SSS	Symptom Severity Scale
THC	Tetrahydrocannabinol
WP2019	Widespread Pain Index 2019
1RM	One Repetition Maximum
2-AG	2-Arachidonoylglycerol
5-HTP	Amino acid 5-hydroxytryptophan

1. Chapter One: Literature Review

Fibromyalgia is a syndrome whereby low-grade immunoinflammatory responses, sensory processing and muscle contractile functions are altered (Andres-Rodriguez et al., 2019). Alterations in sensory fibres, sensory-motor controls, and corticoid sensory processing contribute to somatic disassociation, neuropathic pain, and central sensitization (Staud & Smitherman, 2002). To reduce the severity of fibromyalgia signs and symptoms, pharmacotherapies are commonly prescribed, for example, anti-depressants, anticonvulsants, tramadol (an analgesic), and cannabinoids (Kia & Choy, 2017). However, efficacy of these therapies is reported as low to moderate (Kia & Choy, 2017; Rico-Villademoros et al., 2020). Non-pharmacological treatments prescribed for fibromyalgia include physical therapy, and cognitive behavioural therapy are first-line treatments (Kia & Choy, 2017). Physical activity and psychological treatments are preferred for fibromyalgia symptoms over pharmacologic therapies, as they provide superior effects on overall health outcomes and well-being. There is also promise for certain dietary modifications for treating common fibromyalgia comorbidities (Correa-Rodriguez et al., 2019).Complexities of this condition make pharmacological and lifestyle interventions challenging.

Fibromyalgia is a member of central sensitization syndromes, which includes irritable bowel syndrome and chronic fatigue syndrome (Yunus, 2012). Fibromyalgia affects roughly 1.7-5% of the population (Tzadok & Ablin, 2020), and has previously been overestimated in women, showing 90% of surveying participants to be women (Ablin et al., 2012; Azevedo et al., 2012; Wolfe et al., 2018). However, in 2016 the fibromyalgia criteria were re-classification and the female to male sex ratio has since reduced to < 60% (~1.5:1) from previously reported (9:1) (Tzadok & Ablin, 2020; Wolfe et al., 2018). Fibromyalgia is found worldwide across the lifespan and is included on the national disability insurance scheme (NDIS) in Australia (Neumann & Buskila, 2003).

Fibromyalgia symptoms include widespread musculoskeletal nociplastic pain (Trouvin & Perrot, 2019), chronic fatigue (Almulla et al., 2020), depression and anxiety (Taylor et al., 2020; Hernandez-Leon et al., 2018; Theoharides et al., 2019), pain catastrophizing (Galvez-Sanchez et al., 2020) and suicidal ideation (Levine & Horesh, 2020). Fibromyalgia symptoms are commonly associated with comorbidities including gastrointestinal disorders (Clos-Garcia et al., 2019), major depressive disorder (Carta et al., 2018), blunted cardiovascular reactivity (Gonzalez et al., 2019), insomnia (Cervilla et al., 2019), obesity (D'Onghia et al., 2021), sexual dysfunction (Besiroglu & Dursun, 2019) and temperature dysregulation (Larson et al., 2014).

Fibromyalgia symptoms can be interpreted as physiological compensatory mechanisms to altered sensory networks. These networks are damaged by release of neuro-sensitizing molecules which stimulate thalamic microglia (Theoharides et al., 2019). Physical activity is avoided due to the pain and can result in loss of sensory-motor command accuracy (Brun et al., 2020).

Neuropsychological symptoms of fibromyalgia have previously been misinterpreted as primarily psychosis, not necessarily considered a somatosensory dysfunction (Fitzcharles et al., 2013). This simplistic perspective of the condition is problematic when providing holistic interventions to mitigate symptoms. Stigmas associated with psychological disorders bring societal shame, possibly reducing adherence to regular health care, social support, and successful rehabilitation (Cândea & Szentagotai-Tătar, 2018). The current interdisciplinary classification of fibromyalgia is stated to be a cluster of symptoms not found in other somatic or psychological conditions (Fitzcharles et al., 2013). The comorbid mental illness is a major depressive disorder (MDD), although patients with fibromyalgia may experience anxiety and depression, they may not meet the criteria for a MDD diagnosis. Nociplastic pain can present as anxiety and depression symptoms, therefore there may be an overlap in symptom and comorbidities. Therefore, treatment for this condition must include strategies to address all symptoms presented, especially whereby distress and trauma is a contributing factor to disease development, such as psychological distress and suicidal ideation (Hauser et al., 2015; Ordóñez-Carrasco et al., 2020). Those diagnosed with fibromyalgia present with symptoms of depression, and it is common for fibromyalgia patients to be prescribed anti-depressant pharmacotherapies (Kia & Choy, 2017). Anti-depressants, however, provide acute relief from depressive symptoms but do not address the physiological cause of depression (Córdova-Palomera et al., 2015). The resting state of the amygdala is said to be a contributing mechanism by which depression is developed (Córdova-Palomera et al., 2015). The amygdala prompts the posterior pituitary to produce the cortico-releasing hormone in response to visual and tactile sensory information (Córdova-Palomera et al., 2015). This mechanism is also accompanied by a lack of norepinephrine and serotonin release, reducing biochemical processors for parasympathetic functions and feelings of wellness (Delgado & Moreno, 2000).

Symptoms associated with fibromyalgia are due to a range of determinants that influence catecholamine release, voltage gate threshold overflow and proliferation of action potential proteins (Riva et al., 2012). Additionally, severe environmental stressors such as traumatic events and emotional invalidation during developmental years can influence neuronal development and thalamic sensory processing, contributing to subjective responses in pain (Arnett et al., 2019). Pain catastrophizing is a coping mechanism adopted by those who suffer from chronic pain, the main symptom of fibromyalgia that causes a lack of perceived wellness (Galvez-Sanchez et al., 2020). This coping mechanism is developed to mitigate the onset of anxiety, offsetting the risk of a potential panic attack (Galvez-Sanchez et al., 2020). Anxiety disorders, attention-deficit hyperactivity disorder and post-traumatic stress disorder are associated with fibromyalgia and treated with a variety of pharmacotherapies (Coppens et al., 2017; Kia & Choy, 2017). Symptoms of anxiety can range from irritability, hyper-activity, impulsivity and to the advanced stage disorder agoraphobia (Crocq, 2017; Karaş et al., 2020).

Suicidal ideation is a psychological side effect of fibromyalgia nociplastic pain, and those who suffer chronic pain are considered high-risk suicidal groups (Ordóñez-Carrasco et al., 2020). In their study of suicide ideation risk in those with fibromyalgia Ordóñez-Carrasco et al. (2020) identified that moderate to high degrees of physical dysfunction accompanied with high levels of burdensomeness and high scores of disease severity are associated with a higher risk of suicidal ideation. A higher degree of physical dysfunction in an individual with fibromyalgia increases the risk of suicidal ideation (Ordóñez-Carrasco et al., 2020). It is vital for this cohort to mitigate pain symptoms early in hopes to reduce the risk of disease progression and suicidal ideation.

Diagnosis of fibromyalgia is commonly accompanied with comorbidities including, but not limited to, arthritis (Sayın et al., 2020), irritable bowel syndrome (Erdrich et al., 2020), obesity (Aloush, 2019), costochondritis (Mukerji et al., 1995), attention deficit hyperactivity disorder (Karaş et al., 2020), psychological stress (Pagliusi et al., 2020), temporomandibular disorder (Costa et al., 2017), pelvic floor dysfunction (Carrillo-Izquierdo et al., 2018), and systemic lupus erythematosus (Neumann & Buskila, 2003). Additionally, a fibromyalgia diagnosis left untreated can increase the risk of developing other diseases, such as cancer and diabetes (Afrisham et al., 2019).

The pathophysiology of fibromyalgia is complex and determined by the aetiology, whether top-down (psychological and emotional distress) or bottom-up (sensory, motor, and hormonal) pathways. Commonly the pathophysiology of fibromyalgia involves immune (Gonzalez-Vives et al., 2019) and neurological pathway alterations (Albrecht et al., 2019; Andres-Rodriguez et al., 2019).

Symptoms of fibromyalgia point toward the hypothesis of neuroinflammation. For instance, Albrecht et al. (2019) compared positron emission tomography scans of 31 fibromyalgia patients to 27 healthy controls and observed elevated glial cell activation in the lateral and medial regions of the frontal and parietal lobes of the fibromyalgia group. Additionally Albrecht et al. (2019) found an association with higher self-reported fatigue levels in the fibromyalgia group and microglial activation in the anterior and posterior middle cingulate cortices, influencing pain and memory processing. Low basal cortisol expressions are also seen in fibromyalgia studies (Gonzalez-Vives et al., 2019). These blunted hormone secretions and hypersecretion of substance P, tumour necrosis factor-alpha, hemokinin-1 and calcitonin-gene related peptide result in low-grade immune activation (Theoharides et al., 2019). In response, thalamic mast cells are stimulated with higher frequency and hyper-degranulate (Figure.1-1)(Theoharides et al., 2019). Accordingly, there are lower secretions of known anti-inflammatory cytokines interleukin 10 and chemokine ligand 8 (Andres-Rodriguez et al., 2019). These alterations to chemical pain processing and sensory mechanisms dampen growth hormone and digestive hormone secretions, favouring pro-inflammatory feedback loop by releasing corticotropin releasing hormone (Frieboes et al., 2004).

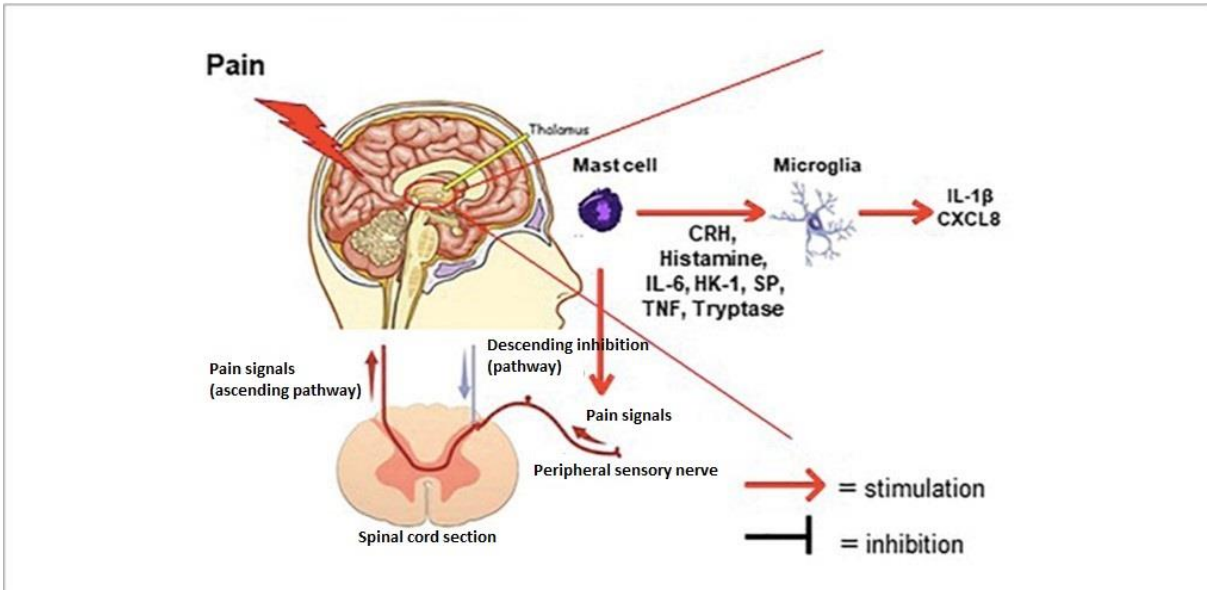


Figure 1-1. Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome. (Theoharides et al., 2019).

Fibromyalgia has been proposed as a clinical endocannabinoid deficiency (CED). CED is the proposed cause of underlying centralised pain conditions, evidenced by hypo-functioning endocannabinoid systems (ECS) (Russo, 2016 (a)). The ECS modulates chemical homeostasis in central and peripheral nervous systems by synaptic repolarization of action potentials and chemical signalling (Guo & Ikeda, 2004). In a dysfunctional state, these retrograde functions are altered, and pain sensations are enhanced (Russo, 2016 (a)). In healthy individuals, fibres descending supraspinal regions can also control pain by inhibition where the endocannabinoid tone is balanced (Moayedi & Davis, 2013; Russo, 2016 (a)). However, in central sensitization and fibromyalgia, this mechanism is suppressed (Theoharides et al., 2019).

Persistent widespread musculoskeletal pain is the primary symptom of fibromyalgia which has the most impact on daily activities, reducing the quality of life and physically altering muscle function and posture of the sufferer (Sempere-Rubio et al., 2018). The physical manifestation of fibromyalgia pain is seen in the development of kyphosis and lower back pain (Sempere-Rubio et al., 2018). In this state, global muscles compensate for the weakened postural muscles and become dysfunctional (Sempere-Rubio et al., 2018). This postural compensation compromises coordination increasing the risk of falls and the impact of breaking forces on ankles, knees, and hip joints, contributing to the risk of developing osteoarthritis (Heredia-Jimenez et al., 2016). Circulation is also compromised in abnormal posture resulting in injury by hypoxia to the midbrain, circle of Willis and descending sympathetic tract (Zhang et al., 2014).

Fatigue is another symptom of fibromyalgia that reduces the quality of life and, when accompanied by intense pain symptoms, reduces the individual's physical function (Vincent et al., 2013). In addition, muscle fatigue and limited physical endurance are symptoms of fibromyalgia that increase the risk of muscle mass loss and physical dysfunction (Dailey et al., 2016).

The varied accumulation of the pathophysiology associated with loss of muscle function and nociplastic pain enhances the development of central sensitization (Hazra et al., 2020). These disease manifestations are seen in lower pressure pain thresholds, serum biomarker levels, mineral deficiencies, and neuroimaging of cortical grey matter (Boehme et al., 2020).

Higher volumes of corticosteroids are present within the pathophysiology of fibromyalgia (Bäckryd et al., 2017). Excess release of these steroids and reduced secretions of inhibitory neurotransmitter gamma-aminobutyric acid injures peripheral A and C nociceptors developing nociplastic pain and lowering pain tolerance thresholds (Moayedi & Davis, 2013).

Pressure pain threshold testing identifies peripheral pain thresholds and tenderness of specific points on the body by algometer measurement (Cheatham et al., 2018). Correa-Rodriguez et al. (2019) measured pressure pain thresholds in a fibromyalgia cohort (n = 95) and compared them to healthy controls (n = 98) and found that the fibromyalgia group experienced an earlier onset of pain with pressure application. Andres-Rodriguez et al. (2019) compared biomarkers of inflammation (interleukin 6 and 10, and chemokine ligand 8) in n = 66 fibromyalgia diagnosed participants compared to n = 35 healthy controls and found that the fibromyalgia group had lower signalling of biomarkers interleukin 10 and 6. Authors suggest that the lack of the neuroprotective mechanisms of these cytokines may indicate an explanation for fibromyalgia symptoms, however, more research on larger sample sizes, included males, is needed (Andres-Rodriguez et al., 2019). Mineral deficiencies (magnesium, iron, and calcium) are also reported to be part of the pathophysiology of fibromyalgia (Kim et al., 2011).

Central pain processing is altered in fibromyalgia cohorts, evidenced by the reduced density of cortical grey matter within the anterior insular and hippocampus (Boehme et al., 2020). For instance, Boehme et al. (2020) investigated functional imaging of 31 patients with fibromyalgia who presented with opposite insular activity compared to healthy controls during fast and slow brush strokes to the skin (Figure.1-2). The result of this feedback loop in fibromyalgia upregulates genes associated with pain processing, mental disorders, immune disease, and musculoskeletal diseases (Qiu et al., 2020).

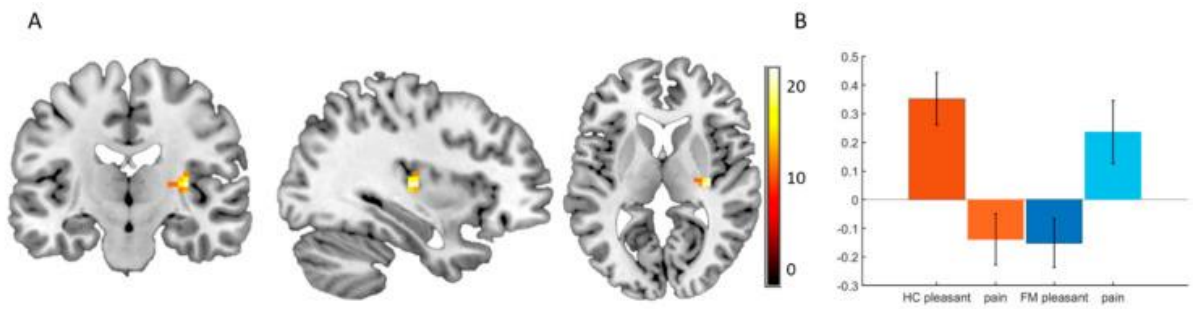


Figure 1-2. Insula activity differs between fibromyalgia patients and healthy control group during rating period (Boehme et al., 2020).

Diagnosis of fibromyalgia is complex and involves testing for hypersensitivity to pain, psychological testing, and monitoring. Patients may not qualify for some American College of Rheumatology (ACR) criteria for a fibromyalgia diagnosis, although they may present with several other symptoms or comorbidities associated with a fibromyalgia diagnosis (Yunus, 2012). A general practitioner or Rheumatologist can diagnose fibromyalgia if patients meet the ACR revised criteria (Wolfe et al., 2016).

In 1990, the ACR fibromyalgia criteria included examination of tender points at multiple regions of the body, a score of >11 of 18 tender points over five regions of the body that are present with no physical abnormalities, and persistent pain for over three months (Wolfe et al., 1990). These diagnostic criteria were reviewed in 2010 to determine a less invasive diagnosis examination. They resulted in including the Widespread Pain Index and Symptoms Severity Scale measures, reducing the need to measure tender points (Wolfe et al., 2010). In addition, to minimise fibromyalgia diagnosis misclassification, a review of the criteria in 2016 provided quantitative validation of the 2010 reviewed criteria (Wolfe et al., 2016). Other measurements used to identify the severity of symptoms include the Revised Fibromyalgia Impact Questionnaire (FIQR), Symptom Severity Scale (SSS), Polysymptomatic Distress Scale (PDS), the Hospital Anxiety Score (HAS) and the Widespread Pain Index (WPI) (Wolfe et al., 2019; Wolfe et al., 1990).

Fibromyalgia is difficult to manage and, unfortunately, is usually concurrent with comorbidities that reduce quality of life (Carta et al., 2018). Long-term outcomes of poorly managed fibromyalgia symptoms increase susceptibility in developing other life-threatening diseases such as diabetes mellitus and cancer (Afrisham et al., 2019). Finding the most appropriate intervention for these symptoms is vital to mitigate the increasing severity of the disease.

Treatments and Management

There are a number of therapies prescribed to treat the signs and symptoms of fibromyalgia, which include physical therapy and cognitive behavioural therapy (Kia & Choy, 2017). Pharmacotherapies such as anti-depressants, anti-convulsant, opioids, cannabinoids, and muscle relaxants are also

recommended for fibromyalgia treatment (Kia & Choy, 2017). There are also dietary modifications that individuals with fibromyalgia can adopt that may help manage the severity of fibromyalgia comorbidities, for example, obesity (Hall & Kahan, 2018). Due to the complex nature and development of the disease, managing fibromyalgia signs and symptoms is difficult and requires careful deliberation of the appropriate therapy for the individual.

Recommending guidelines for fibromyalgia pharmacological treatments are continually under review as new findings on pharmacotherapies and combinations of drugs are unearthed. In their review of pharmacotherapies for fibromyalgia, (Kia & Choy, 2017) included recommendations by international committees for pain conditions: the European League Against Rheumatism (EULAR), Canadian Pain Society (CFGC) and the Scientific Medical Societies in Germany (AWMF); and the most common drugs to be prescribed for fibromyalgia were identified (Table 1-1). These drugs include amitriptyline, pregabalin and duloxetine. Although these drugs have varying degrees of high-quality evidence for their prescription (Table 1-2) an emerging class of drug for treating fibromyalgia symptoms are cannabinoids. Cannabinoids may provide analgesic and anti-anxiolytic effects and appear safe and effective for the treatment of fibromyalgia symptoms (Sagy et al., 2019).

Recommended durations for how long a pharmacotherapy should be prescribed for a person with fibromyalgia are poorly defined. In their review, Kia & Choy (2017), provide a statement, “the therapy should be changed or stopped if no effect is observed”. Other than this statement, there is little information available on the recommendations for the duration of prescribed pharmacotherapy.

Therapy	AWMF	CFGC	EULAR	FDA	Reviewed Studies
Amitriptyline	Strong recommendation (10-50mg daily)	Low recommendation	Low recommendation	Not recommended	AWMF: 12 studies in metanalysis, CFGC: 2 reviews, EULAR 5 reviews
Anticonvulsants (Pregabalin PGB, Gabapentin GBP)	PGB recommended (150-450mg daily) when AMT n/a, no information on GBP	Strong recommendation	Low recommendation for PGB	Recommended (no dose)	EULAR: 9 reviews on PGB, one clinical trial of GBP (GBP recommended for research only)
SNRI (Duloxetine DLX, Milnacipran MLN)	DLX recommended (60mg daily), MLN not recommended	DLX recommended (60mg daily)	DLX recommended (60mg daily)	Recommended (no dose)	EULAR: 8 systematic DLX reviews, 7 MLN systematic reviews
Fluoxetine	Recommended (20-40mg daily)	Do recommend (20-40mg daily)	Not recommended	Not recommended	EULAR: 7 systematic reviews, AWMF: 8 RCT in meta-analysis,
Tramadol	Not recommended	Recommended (no dose)	Recommend (no dose)	Recommended	EULAR: 2 meta-analysis, Canadian: 2 RCT, AWMF: 1 RCT
Cyclobenzaprine	Not recommended	Not recommended	Not recommended	Not recommended	EULAR: 1 systematic review
Cannabinoids	Not recommended	Recommended (no dose)	Not recommended	Not recommended	Not available
Acetaminophen	May be beneficial, not enough data	May be beneficial, not enough data	May be beneficial, not enough data	Not recommended	EULAR: Commonly used in combination with tramadol, DLX and PGB for severe pain
NSAIDs	Not recommended	Recommended (low dose for comorbidity of OA)	Not recommended	Not recommended	Not available

Table 1-1. Table 1-1. Generated from data obtained from Kia & Choy (2017). European League Against Rheumatism (EULAR), Canadian Pain Society (CFGC) and the Scientific Medical Societies in Germany (AWMF), Food and Drug Association (FDA). Non-steroidal anti-inflammatory drugs (NSAIDs), Osteoarthritis (OA), Cognitive Behavioural Therapy (CBT), Randomised Control Trial (RCT), Milnacipran (MLN), Duloxetine (DLX), Pregabalin (PGB) and Gabapentin (GPB), Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), Not Applicable (N/A).

Drugs for Treating Fibromyalgia Symptoms

Amitriptyline (also known as Endep), Duloxetine, Milnacipran

Drug Class: Anti-depressants

Serotonin and noradrenalin reuptake inhibitors are a class of drug that is known to relieve tension headaches, migraines and anxiety that are associated with post-traumatic stress disorder and fibromyalgia (Thour & Marwaha, 2021). There is some benefit in the use of serotonin and noradrenalin reuptake inhibitors for fibromyalgia pain frequency and global impression scores (Welsch et al., 2018). A meta-analysis of randomised control trials of serotonin and noradrenalin reuptake inhibitors on fibromyalgia participants by Welsch et al. (2018) identified that when

duloxetine and milnacipran are used in combination, a reduction in pain frequency of > 30% was observed (n = 888 of 1710, 95% confidence interval (CI): 0.08 to 0.12: number needed to treat benefit, 10; 95% CI: 8 to 12), but no benefit for fatigue was reported. The review by Welsch et al. (2018) also identified the lack of high-quality evidence for this drug class for symptoms of pain intensity, fatigue, and sleep quality, which has been suggested as the reason why the Food and Drug Administration (FDA) does not recommend this drug for fibromyalgia (Kia & Choy, 2017). Side effects include weight gain, gastrointestinal upset, headache, and somnolence (Thour & Marwaha, 2021).

Amitriptyline is a tricyclic antidepressant that is commonly prescribed for fibromyalgia pain symptoms, as this class of drug has multiple pharmacologic targets and is well tolerated in fibromyalgia studies (Rico-Villademoros et al., 2015). Furthermore, the combination of cardiovascular exercise training and amitriptyline (dosed at 25 mg/day) was found to be superior to either treatment taken in isolation. However, amitriptyline did not provide benefit in reduction of Fibromyalgia Impact Questionnaire results compared to psychological interventions of relaxation techniques with imagery, when dosed at 50 mg/day over four weeks.

Gabapentin and Pregabalin, also known as Lyrica

Drug Class: Anti-convulsant

Anti-convulsant drugs gabapentin and pregabalin are drugs structurally similar to gamma-aminobutyric acid (Cooper et al., 2017). It was once thought that this class of drugs provided inhibitory effects like gamma-aminobutyric acid as they are structurally similar. However, there are no evidenced interactions with the associated receptors for gamma-aminobutyric acid (Bethesda, 2020). For the symptoms of fibromyalgia, gabapentin is prescribed to reduce the intensity of pain (Arnold et al., 2007), although there is a lack of high-quality evidence for their efficacy (Cooper et al., 2017).

In contrast to gabapentin, a review of the efficacy of pregabalin for the neuropathic pain symptoms in fibromyalgia Derry et al. (2016) identified it as effective in reducing pain intensity in people with moderate to severe fibromyalgia pain and supported by high-quality evidence. Supplementation of 450 mg of pregabalin by 3,283 participants (5 studies) was reported by 1,874 participants to have a 50% reduction in pain intensity at 13 weeks of stable treatment (risk ratio 1.8, 95% CI: 1.4 to 2.1) (Derry et al., 2016). Adverse side-effects reported include weight gain, peripheral oedema, drowsiness, and sexual dysfunction (Derry et al., 2016; Hamed, 2018).

Paracetamol, Non-steroidal Anti-inflammatory Drugs (NSAID's), Oxycodone, Tapentadol and Tramadol

Drug Class: Analgesic

Paracetamol is an over-the-counter analgesic (in Australia) that targets pain by central inhibition of prostaglandin synthesis (Abdel Shaheed et al., 2021). Paracetamol is commonly added to cold and flu medication and is typically taken to reduce the severity of tension-type headaches (Abdel Shaheed et al., 2021). Paracetamol is safe when used in combination with tramadol. In a randomised, placebo controlled study, 157 out-patients reported reductions in fibromyalgia pain, measured by visual analogue scores of pain (53 +/- 32 vs 65 +/- 29) and fibromyalgia impact questionnaire scores ($p = 0.008$), when dosed at 37.5 mg/d of tramadol combined with 325 mg/day of paracetamol over 91 days (Bennett et al., 2003). Adverse side effects associated with paracetamol include induced respiratory depression, hypertension, tachycardia, headache, nausea, and vomiting (MIMS, 2020).

Non-steroidal anti-inflammatories (NSAIDs) provide peripheral inhibition of cyclooxygenase and prostaglandin. Etoricoxib, Ibuprofen, Naproxen, and Tenoxicam are prescribed for fibromyalgia pain symptoms (Derry et al., 2017), although there is a lack of high-quality evidence supporting their prescription. In the review of NSAIDs for fibromyalgia pain compared to placebo (Derry et al., 2017) reported no significant results for NSAIDs providing a reduction in pain intensity superior to placebo. Digested in the gastrointestinal tract and metabolised in the liver, non-steroidal anti-inflammatories have a high affinity to plasma proteins. Therefore, contraindications include issues with the digestive tract (García-Rayado et al., 2018). It is not advised that those who are asthmatic, have hypertension, are pregnant, suffer head colds, and who are taking aspirin or anti-inflammatory medications take NSAIDs, as it may result in adverse side effects in kidney and liver functions, including skin rashes, skin blisters, diarrhoea, vomiting, blood in stools and oedema (Tai & McAlindon, 2018). Used long term, NSAIDs can also place the patient at risk of cardiovascular disease (García-Rayado et al., 2018). Oxycodone is a class of opioid drug that provides analgesic effects by agonist effects on opioid receptors, with weak affinity to kappa and delta receptors of the central nervous system and smooth muscle (Gaskell et al., 2016). Oxycodone is a schedule two drug that has a risk of physical and psychological dependence (Preuss et al., 2021). Stronger opioids, fentanyl and morphine are not recommended for the treatment of fibromyalgia pain (Kia & Choy, 2017).

Tapentadol is an opioid receptor agonist and norepinephrine reuptake inhibitor commonly prescribed to reduce disease progression of neuropathic pain conditions, including osteoarthritis, chronic back pain, chronic pelvic pain, and fibromyalgia (Coluzzi et al., 2017). However, there are no systematic reviews nor high-quality evidence clinical trials on the efficacy of Tapentadol for the symptoms of fibromyalgia. Adverse side effects reported with the use of Tapentadol include nausea, vomiting and dry mouth (Niesters et al., 2014).

Tramadol is an analgesic with opioidergic, noradrenergic and serotonergic mechanisms of action that are beneficial for pain conditions (Barakat, 2019); however, there is little evidence of the use of

tramadol in fibromyalgia. Adverse side effects include nausea, dizziness, drowsiness, fatigue, sweating, vomiting, and dry mouth (Barakat, 2019).

Cannabidiol and Palmitoylethanolamide

Drug Class: Anti-spasticity and Anti-inflammatory

Cannabidiol (CBD) is a cannabis-based medicine that is prescribed for the symptoms of chronic pain and inflammation as there are effects on peripheral neural activity, inhibition of fatty acid amino hydrolase, tumour necrosis factor-alpha and interleukin-6 (Petrosino et al., 2018; Schott, 2019; Turcotte et al., 2016). In their prospective observational study of 102 fibromyalgia patients who reported pain > 4 and who were using an analgesic, Giorgi et al. (2020), reported improvements in fatigue (Mean 7.727, SD 2.421), pain (mean 3.098, SD 2.208) and sleep (mean 7.470, SD 2.488). Although there is limited data for meta-analysis for medicinal cannabis interventions for symptoms of fibromyalgia pain (Berger et al., 2020). In a prospective observational study of fibromyalgia patients and cannabinoid use, Sagy et al. (2019) reported significantly reduced 10-point scale ratings (mean score from 9 to 5) associated with cannabinoid use. Adverse events reported with cannabis products include dizziness, headache, somnolence, confusion, paranoia, and substance dependence (Mücke et al., 2018; Russo, 2016 (b)).

Palmitoylethanolamide (PEA) is an n-acylethanolamine phospholipid found in dietary fats (Beggiato et al., 2019), which has anti-inflammatory properties through inhibition of caspace-3 and prostaglandin and stimulation of nuclear peroxisome proliferator-activated receptor-alpha (PPARα) protein synthesis (Guida et al., 2017; Skaper et al., 2015). Del Giorno et al. (2015) observed in their 6-month observational study of a fibromyalgia cohort (n = 80) that PEA supplemented in addition to duloxetine and pregabalin significantly reduced scores of tender point pain thresholds. Side effects of PEA are reported to be gastrointestinal upset, drowsiness, headache, restlessness, and skin irritation (Beggiato et al., 2019).

Pharmacotherapies Prescribed for Fibromyalgia Pain			
Therapy	**Mode of action**	**Adverse Side Effects**	**Reference**
Serotonin and noradrenalin reuptake inhibitors: Amitriptyline, Duloxetine	Inhibit reuptake of serotonin and noradrenalin	Mania, suicide, anxiety, depression, renal impairment, seizures, dependency, allergic reactions, hypertension, tachycardia, fatigue, constipation	Hossain et al. (2016); Kia and Choy (2017); Thour and Marwaha (2020); Thour and Marwaha (2021)
Anticonvulsants: Gabapentin, Pregabalin	Inhibit ion-gated calcium channels	Suicidal thoughts, fatigue, cardiotoxicity, loss of sexual function	Awwad et al. (2019), Besiroglu and Dursun (2019);Cooper et al. (2017); Derry et al. (2016); Hamed (2018); Kia and Choy (2017); Wiffen et al. (2017)
Analgesic: Non-steroidal anti-inflammatories	Inhibit COX-1 and COX-2 receptors	Gastrointestinal damage	García-Rayado et al. (2018); Tai and McAlindon (2018)
Analgesic: Oxycodone, Tapentadol	Bind to central and peripheral G protein-coupled receptors; mu, kappa, and delta	Dependency, respiratory depression, fatigue, constipation, convulsive disorders, coma	Chartoff and Connery (2014); Kia and Choy (2017); Reyes et al. (2020); Stannard (2016); Wang et al. (2019)
Analgesic: Paracetamol	Activation of descending serotonergic pathways	Hypertension, tachycardia, headaches, nausea, vomiting	Abdel Shaheed et al. (2021); Saragiotto et al. (2016): Anderson et al. (2008)
Analgesic: Tramadol	Inhibit reuptake of noradrenalin and serotonin and weak inhibition of opioid activity	Nausea, dizziness, drowsiness, fatigue, sweating, vomiting, and dry mouth	Barakat et al., (2019)
Anti-inflammatory: Cannabidiol (CBD)	Inhibit reuptake of excitatory neurotransmission, fatty acid amino hydrolase, tumour necrosis factor alpha and interleukin-6	Gastrointestinal upset, dry mouth, fatigue, drowsiness, headache, restlessness, sedation, skin irritation, tachycardia, hypotension	Franco and Perucca (2019); Hughes and Herron (2019); Mücke et al. (2018); Murillo-Rodríguez et al. (2008); Olivas-Aguirre et al. (2019); Russo (2016 (b))
Anti-inflammatory: Palmitoylethanolamide (PEA)	Inhibit caspace-3 and prostaglandin	Gastrointestinal upset, drowsiness, heart palpitations, skin irritation	Beggiato et al. (2019); Couch et al. (2017); Gabrielsson et al. (2017); (Skaper et al., 2015); Vittorio et al. (2019)

Table 1-2. Pharmacotherapies prescribed for fibromyalgia. COX-1,COX-2: Cyclooxygenase.

Medications targeted to relieve neuropathic pain symptoms, fluctuations in psychological symptoms and increase relaxation for sleep are prescribed for fibromyalgia (Hsu, 2011). However, there is a risk of these pharmacological treatments being ineffective over placebo in some individuals (Welsch et al., 2018). Additionally, taking pharmacological therapy for pain comes with a risk of adverse side effects, including dependence (Preuss et al., 2021). Long-term use of pharmacotherapies is also associated with and may place those with fibromyalgia at risk of developing movement disorders (Zesiewicz & Sullivan, 2011). A non-pharmacological treatment recommended as first-line treatment for fibromyalgia that has less associated risk, and other beneficial effects on health and well-being, is physical activity (Kia & Choy, 2017).

Exercise Therapy for Fibromyalgia

Physical activity is recommended as a daily activity for maintaining health (Department of Health, 2021). The Australian Federal Government Department of Health exercise guidelines for healthy populations (18 to 65 years) recommend minimising sedentary time and maximising physical activity on most days of the week, including two resistance (strength) training sessions per week (Department of Health, 2021). The guidelines recommend reaching 150-300 minutes of moderate intensity (3-5 on the Borg Rate of Perceived Exertion scale) per week to maintain health (Williams, 2017).

Respiratory rates are compromised in fibromyalgia which can exacerbate symptoms of pain, fatigue, and anxiety (Tomas-Carus et al., 2018). As a result, controlled breathing from physical exercise assists in regulating ventilated outputs by maintaining the oxygen-carbon dioxide balance and increasing mechanoreceptor sensitivity (Agostoni et al., 2017). Resistance (strength) exercise also assists in regulating neuroimmune functions by secretion of myokine interleukin 6 in response to exercise, which promotes anti-inflammatory mechanisms (Daou, 2020). Longitudinal data identifies that those with fibromyalgia who partake in regular physical activity have improved quality of life scores, including an elevated sense of belonging and feelings of strength (Izquierdo-Alventosa et al., 2020).

Fibromyalgia pain and fatigue symptoms place those at risk of physical dysfunction. For instance, Dailey et al. (2016) collected data of 94 fibromyalgia participants and found reported increases in pain and fatigue intensity scores resulted in a lack of physical performance of the 6-minute walk test and 5-sit to stand test. Physical activity is, however, shown to be a successful tool for reducing fatigue scores in fibromyalgia participants. Ericsson et al. (2016) trialled a resistance exercise protocol on 130 women with fibromyalgia and found improvements from baseline to post-treatment (15 weeks) in mental (10.7%), physical (10.6%) and general fatigue (7.5%) scores. These effects, however, only occurred in lean participants as there were varied responses in participants who were obese (Ericsson et al., 2016). Additionally, Ericsson et al. (2016) did not report medications use which may have influenced scores of fatigue in the obese participants.

Obesity is a comorbidity of fibromyalgia that influences proinflammatory pathways and exacerbates pain symptoms (D'Onghia et al., 2021). The problem for those who have high body mass indexes and diagnosis of fibromyalgia is that physical activity is often difficult and painful (Kapuczinski et al., 2021). In a Spanish fibromyalgia cohort, performing light daily physical activity was correlated with higher rates of productive (housework and childcare) work and moderate to vigorous activity showed fewer rates of productive work (Alvarez-Gallardo et al., 2019). Authors from this study collected physical fitness data, however, they did not report on whether physical fitness had an association with productive work levels (Alvarez-Gallardo et al., 2019). Therefore, it is unknown whether existing levels of fitness affect productivity following exercise training. Those who are diagnosed with fibromyalgia are at risk of weight gain and obesity (D'Onghia et al., 2021) and so the combination of physical activity in parallel to dietary modification (which can be effective in aiding weight management) may be the best approach to support the overall management of fibromyalgia symptoms and risk of development of comorbidities.

Diet Change for Fibromyalgia Management

Those who are diagnosed with fibromyalgia are at risk of weight gain and obesity (Udit et al., 2017), and so the combination of physical activity in parallel to dietary modification (which can be effective in aiding weight management) may be the best approach to support the overall management of fibromyalgia symptoms and risk of development of comorbidities. In the pathophysiology of fibromyalgia, sensory-motor activity and immune functions are blunted from excess pro-inflammatory mechanisms (Andres-Rodriguez et al., 2019). These functions include the innervation of vagal afferent neurons in the gastrointestinal tract (Russo, 2016 (a)). Dietary intakes high in saturated fat and sugar are considered detrimental for gastrointestinal health; therefore excluding these items from the diet could benefit fibromyalgia symptoms and comorbidities (Department of Health, 2020). For instance, the Australian Dietary Guidelines suggests minimising the intake of high sugar and high-fat items daily to maintain health (Department of Health, 2020). However, it is unknown Australians with fibromyalgia eat according to these guidelines or whether their diets are detrimental to their symptoms.

There is evidence that diets high in saturated fats and sugar can activate microglial cells in the gastrointestinal tract, reducing the diversity of microbiota and promote vagal nerve remodelling (Cawthon & de La Serre, 2018). For those diagnosed with fibromyalgia a poor diet combined with central sensitisation could provide an explanation for blunted immune responses. For instance, in their experimental study on mice that were desensitised by removal of sensory neurons and fed a high (saturated) fat diet, (Udit et al., 2017) reported the high fat diet compared to control chow diet promoted elevated levels of interleukin 6, fluctuations in weight, spleen enlargement, and an

increased antibody count for lipopolysaccharides. Individuals managing fibromyalgia symptoms via diet may find a diet high in plant-based foods and limited intake of saturated fats may aid symptoms.

A high body mass index and high intake of dietary fats is evidenced to lower pressure pain thresholds in fibromyalgia cohorts (Correa-Rodriguez et al., 2019). Dietary fats are categorised as high on the dietary inflammatory index score, which identifies certain foods and their impact on inflammatory factors (Correa-Rodriguez et al., 2019). High intake of saturated dietary fats may also contribute to detrimental effects on the enteric endocannabinoid system and hormone secretions (Russo, 2016 (a)).

Leptin is a hormonal enzyme that is secreted to induce satiety, stimulated by in-tact mechanoreceptors in healthy populations (Mazzuoli-Weber & Schemann, 2015). In mice models of impaired Nav1.8-expressing primary afferent sensory neurons, exaggerated inflammatory responses were developed (Udit et al., 2017). An increase in interleukin 6 secretions, weight fluctuations, hepatic serum amyloid A plasma levels and spleen enlargement ($p=0.0228$) compared to control mice (Udit et al., 2017). Intact Nav1.8 afferent sensory neurons in the gastrointestinal tract are integral factors for vagal nerve functions of energy balance and interoceptive feedback loops. (Udit et al., 2017). Dietary modifications have been popularised to solve many health conditions (Sucher et al., 2017). However, there is little evidence that certain diets benefit fibromyalgia symptoms (Lowry et al., 2020). Furthermore, a diet unbalanced in macro-nutrient intakes, such as the combination of the ketogenic diet, low dairy, and low intake of certain carbohydrates, creates a microbiome lacking in diversity which inhibits fermentation of butyrate, a molecule found to aid an unbalanced gut-brain axis (Stilling et al., 2016). The effects of certain dietary intake on pain symptoms are further complicated by the influence of omega 3 (n-3) and 6 (n-6) essential fatty acids. For instance, Charoenwoodhipong et al. (2020) found that dietary intake high in omega 3 (n-3) essential fatty acids were beneficial for reducing symptoms severity scores of lupus erythematous comorbid with fibromyalgia; n-3 intake reduced self-reported sleep disturbance scores (56.5 ± 8.8, 95% CI: –2.0 to –0.2), and reduced fibromyalgia diagnostic criteria measures of pain (51.8 ± 27.0). Where n-3 intake was higher, there was a reduction of fibromyalgia diagnostic criteria by 20% (0.82, 95% CI: 0.66 to 1.02) compared to a diet high in omega 6 fatty acids.

Although there is limited research on fibromyalgia symptoms, there is quality evidence for the use of dietary modifications for the management of irritable bowel syndrome, a fibromyalgia comorbidity (Stahlberg et al., 2018). For instance, Dionne et al. (2018) identified that the gluten free diet and the low fermentable oligo-, di- and monosaccharides and polyols (FODMAPs) diet were successful in reducing global scores of irritable bowel symptoms (relative risk: 0.69, 95% CI: 0.54 to 0.88). However, only low-quality evidence was available for meta-analysis (Dionne et al., 2018).

Another diet that has promise for reducing the severity of fibromyalgia symptoms is the Mediterranean diet (Román et al., 2019). The Mediterranean diet includes high portions of olive oil

compared to other diets and for the symptoms of fibromyalgia the addition of olive oil may be beneficial. For example, Rus et al. (2017) reviewed extra virgin olive oil supplementation and reported improvements in the fibromyalgia impact questionnaire (median 68.61, (standard error 7.17) to 52.47 (standard error 9.68), ES 0.644, 95% CI: -33.81 to -5.43) and visual analogue scores of pain (median 6.85, (standard error 0.82) to 5.50 (standard error 0.83), ES: 0.384, 95% CI: -3.16 to 1.02)) with a little as three weeks of 50 mL extra virgin olive oil use daily on cohorts with fibromyalgia. The benefits witnessed with olive oil supplementation may be due to its antioxidant effects, however, simply altering the intake of certain foods may not be enough for this population as they are vulnerable to chronic stress (Carta et al., 2018).

Gastrointestinal problems and inflammatory bowel diseases are commonly treated with pharmacotherapy medications to manage digestion and reflux (Derijks et al., 2018). These therapies include amino salicylates, non-steroidal anti-inflammatories, immunosuppressants and corticosteroids to reduce pain and inflammation (Derijks et al., 2018). These pharmacotherapies have an analgesic effects for some, although when used long-term may alter gut microbiome, increase tolerance thresholds, and alter digestive enzymes and hormone secretions (Bertrand et al., 2016). Probiotics may improve these gut microbiome deficiencies. For example, Roman et al. (2018) found eight weeks of probiotic supplementation among 16 fibromyalgia participants tended to reduce visual analogue scores of pain (6.69 ± 0.41 to 5.49 ± 0.38) and the fibromyalgia impact questionnaire scores (60.92 ± 2.90 to 55.06 ± 5.20). These outcomes, while lacking significance, highlight the potential significance for the therapeutic value in a larger cohort.

Nutritional supplements may help reduce the impact of fibromyalgia symptoms (Bjørklund et al., 2018). In their review of nutritional supplements for fibromyalgia, Bjørklund et al. (2018) discussed the value of vitamin B, D, iron, magnesium, and zinc supplementation for addressing common micronutrient deficiencies in fibromyalgia patients. The authors suggest that addressing these deficiencies may reduce the risk of developing obesity and chronic inflammation and provide analgesic effects when used long term, especially in post-menopausal women who have declining oestrogen levels (Bjørklund et al., 2018).

Dietary alterations, including the use of certain supplementations, for example, probiotics and n-3 fatty acids, have promise for improving symptoms of pain and sleep disturbances for those who are diagnosed with fibromyalgia. However, further research studies utilising large sample sizes are required as they are currently lacking in fibromyalgia cohorts. To understand the true benefit of certain diets and dietary supplementation for fibromyalgia patients' future studies of dietary intake, dietary alterations and dietary supplementations should include randomised control trial methods of investigation, that collect serum biomarkers of inflammation and self-reported responses to visual analogue scores of pain and fibromyalgia impact questionnaires in fibromyalgia cohorts. This research

study will fill the current gap in knowledge for successful dietary interventions for fibromyalgia signs and symptoms.

Conclusion

Fibromyalgia is a complex condition that requires interventions via pharmaceutical means and via physical activity to reduce the impact of the disease. Dietary modification may also be beneficial for maintaining good health, although more studies into diet and fibromyalgia symptoms are needed. \ There is a lack of literature in Australians with fibromyalgia focussed on pharmacotherapy, physical activity habits and exercise modalities, daily dietary intake and nutritional supplements used for symptom management.

Therefore, the aim of this Master of Applied Research project is to identify what interventions are used by an Australian fibromyalgia cohort for managing their symptoms of pain. Specifically, this research aims to identify the cohort's prescribed pharmacotherapies for pain, what pharmacotherapies are self- prescribed, what the associated satisfaction scores for pharmacotherapies used are, and what are the overall satisfaction scores for symptom management are. This research also aims to identify the physical activity and exercise habits adopted by the cohort, including the daily dietary habits and modifications made for the management of their fibromyalgia symptoms.

2. Chapter Two: Medication use for Pain in Australians with Fibromyalgia

Abstract

Background:

Fibromyalgia is a disease which is associated with widespread pain. Medications that target chronic pain have varied effectiveness. This study aimed to investigate pharmacotherapeutic pain management strategies used by those who suffer chronic pain as a result of fibromyalgia in Australia.

Methods:

An observational, cross-sectional study was conducted in Australia from August 2020 to September 2020. An online survey was distributed via social media forums and a local pain clinic in Victoria, Australia (Chapter 6 Appendix: Qualtrics Survey Extract). Participants were asked to record symptoms of fibromyalgia, and score satisfactions of prescribed and non-prescribed pharmacotherapies for pain.

Results:

162 participants commenced the survey with 137 completing to the end of the pain questions. Most participants identified themselves as female (female n = 124, male n = 4, other n = 1 completing the entire survey). Respondents reported experiencing pain for 7 days a week (67%), 5-6 days a week (19%), or 3 days a week or less (13%). Other significant symptom characteristics reported by of this cohort was depression (74%), suicidal thoughts (39%) and thoughts of self-harm (32%). The average number of pain medications prescribed was 3.3 per respondent. Medications prescribed to treat pain symptoms were reported as; paracetamol (66%), amitriptyline (58%), duloxetine (38%), pregabalin (31%), tramadol (29%), oxycodone (24%), Palmitoylethanolamide (12%), Tapentadol (9%) cannabidiol (CBD; 7%), and medicinal cannabis (6%). The magnitude of self-reported pain after taking the prescribed medication included no pain (3%), low level mild pain (9%), moderate pain (59%), distressing pain (29%) and extreme pain (1%). A large percentage of respondents reported the use non-prescribed therapies (100%) which included magnesium (73%), vitamin D (59%), vitamin B (50%), probiotics (49%), CBD oil (19%) and cannabis sativa (16%). Pain rating post cannabis plant or CBD oil use reported by 82% of cannabis sativa and CBD users, was no pain (14%), low level pain (27%), moderate pain (18%), distracting pain (18%) and distressing pain (5%).

Conclusion:

Those diagnosed with fibromyalgia in Australia are commonly prescribed more than three pain medications for the management of their symptoms. Despite using multiple prescribed and non-prescribed therapies, respondents reported regular and high levels of pain and poor mental health.

More research is required to understand the therapeutic value of prescribed and non-prescribed pharmacotherapies in the management of the symptoms of pain in people with fibromyalgia.

Keywords: paracetamol, cannabinoids, cannabis sativa, combination therapy

Introduction

Fibromyalgia is a disease whereby sensory processing and neuromuscular contractile functions are hyper-responsive (Wolfe et al., 1990; Wolfe et al., 2018). Chronic stimulation of these functions is typically concurrent with low-grade inflammation and immunosuppression leading to symptoms of hypersensitivity to physical touch and widespread pain (Wolfe et al., 2019).

Management of fibromyalgia is challenging because of the complex and incompletely understood pathophysiology of the condition (Andres-Rodriguez et al., 2019). Pharmacotherapies that target pain are commonly prescribed for fibromyalgia (Kia & Choy, 2017). Classes of pharmacotherapies targeting the broad pain symptoms seen with fibromyalgia include analgesics, anti-depressants, anti-convulsants, and sedatives (Kia & Choy, 2017). In Australia, examples of commonly prescribed drugs from these classes are paracetamol, amitriptyline, duloxetine, oxycodone, pregabalin and cannabinoids (Kia & Choy, 2017). However, the evidence base for the efficacy of fibromyalgia-related pain reduction for many prescribed pharmacotherapies is limited due to a lack of high-quality studies, and consensus guidelines differ in various regions of the world (Kia & Choy, 2017; Thorpe et al., 2018). In a review of fibromyalgia pharmacotherapy treatment guidelines from international fibromyalgia and pain committees, Kia and Choy (2017) noted that each committee developed differing recommendations. While all the committees found evidence for the beneficial use of some common pain medications, such as amitriptyline, when evaluating other pain medications, the lack of high-quality studies for systematic review and meta-analysis resulted in low-tier evidence to support their use (Kia & Choy, 2017). Furthermore, recommendations for the use of opioids for fibromyalgia pain differ between committees. For example, the European League Against Rheumatism (EULAR) and the Canadian Fibromyalgia Guideline Committee (CFGC) both recommend the use of opioids, such as tramadol (a weak opioid that also inhibits noradrenaline and serotonin reuptake), for severe pain. In contrast, the Association of the Scientific Medical Societies (AWMF) in Germany do not recommend opioid use for fibromyalgia pain (Kia & Choy, 2017). Cannabinoids are recommended by the CFGC to treat severe pain, but not the EULAR and AWMF, who cited lack of evidence for its application (Kia & Choy, 2017).

A consequence of the complex pathophysiology of fibromyalgia and the associated pharmacotherapy treatment options, some of which may have limited effectiveness (Kia & Choy, 2017), is that individuals with fibromyalgia may be utilising a combination of drugs to relieve their pain (Rico-Villademoros et al., 2020). For instance, EULAR recommends the combination of paracetamol, duloxetine and pregabalin for severe pain (Kia & Choy, 2017). Despite this recommendation, there is limited available data on the effectiveness of combination therapy (Thorpe et al., 2018). Importantly, there is a lack of data on the range of concurrently prescribed medications taken by people with fibromyalgia and the satisfaction outcomes of single and combination pharmacotherapies. In an online survey of a Spanish fibromyalgia cohort, Rico-Villademoros et al. (2020) found that 46% of

respondents were taking more than two prescribed medications, tramadol being the most prescribed drug (40%). Despite taking more than one medication, on a 10-point numerical rating satisfaction score, the associated satisfaction outcomes were on average poor (< 4). Interestingly, an intervention study by Del Giorno et al. (2015) investigating the effects of palmitoylethanolamide (PEA) on fibromyalgia pain when combined with duloxetine and pregabalin over 6-months and found greater pain reduction with the combination of all three therapies, suggesting there may be some benefit to certain combinations. However, the actual combinations of medications people with fibromyalgia are utilising is poorly described in the literature.

Cannabinoids have gained attention as a pain management option in other clinical conditions with pain such as cancer (Johal et al., 2020) and gastrointestinal diseases (Katz et al., 2017). Still, they are less well-researched as a pain medication in fibromyalgia. In their review of the efficacy of cannabinoids for non-cancer pain relief, the meta-analysis by Johal et al. (2020) determined that cannabinoids were effective in reducing pain (effect size and 95% confidence interval (95% CI): -0.63 (-0.85 to -0.42)) compared to placebo, however the authors noted low-quality of most included studies. Furthermore, a survey by Ravikoff Allegretti et al. (2013) captured cannabinoid therapy habits for pain and symptom management in American patients with inflammatory bowel disease and discovered 16.4% of respondents reported cannabis sativa 'very helpful' for bloating, abdominal pain, and diarrhoea symptoms. Medicinal cannabis is commonly used in many regions of the world to treat pain symptoms for a range of conditions, including fibromyalgia (Johal et al., 2020). Yet, there is also limited data for their use and efficacy (Cohen et al., 2019; Kia & Choy, 2017; Lintzeris et al., 2020). Despite this lack of evidence, non-prescribed medicinal cannabis use is prevalent in those with various conditions, including pain conditions, mental health, sleep disturbances, neurological, cancer and gastrointestinal conditions (Lintzeris et al., 2020).

In Australia, the use of cannabis products for 'over the counter' pharmacological distribution was prohibited until a change in legislation in November 2020, while medicinal cannabis prescription has been available since 2016. However, the extent of use of cannabis products since these legislative changes, and the typical rates of use of other pain medications, have not yet been characterised in the Australian fibromyalgia population. Given the lack of variation of pain management options, clinical populations may seek pain relief through non-prescribed cannabis (Lintzeris et al., 2020), despite concerns regarding unregulated variability of non-prescribed cannabis and the risk of high tetrahydrocannabinol (THC) and lower cannabidiol (CBD) ratios (Turner et al., 2020). High THC: CBD ratios increase the risk of developing associated adverse psychological side effects when taken (Turner et al., 2020). Therapeutic application of medicinal cannabis and combination therapies as part of the treatment plan for fibromyalgia requires further investigation. Thus, the aim of this study was to understand what a sample of the Australian population with fibromyalgia are being prescribed for

pain, whether this cohort are taking non-prescribed therapies and what their associated satisfaction outcomes are.

Methodology

An observational, cross-sectional study comprising an online questionnaire (Qualtrics) was conducted in Australia from August 2020 to September 2020. A link to the online questionnaire was distributed via social media forums and a local pain clinic. The online questionnaire was developed based on google search engine results for common fibromyalgia terms; drugs for fibromyalgia, treatment for fibromyalgia, exercise for fibromyalgia, supplements for fibromyalgia, and based on the current literature for fibromyalgia symptoms and pharmacotherapy (Kia & Choy, 2017; Wolfe et al., 2019). The target number for participants to be recruited was 120, based on similar fibromyalgia survey response numbers in the literature. The number of questions within the survey altered, depending on the participant's responses (Appendix Qualtrix Survey Extract). Participants who subscribed to Australian fibromyalgia Facebook groups and clients of the pain clinic in Victoria, Australia, were recruited to the survey study. A total of five social media Facebook groups and one pain clinic in Victoria received three posts of the survey advertisement, over four weeks. Participants gave informed consent and completed screening questions to assess eligibility to undertake the questionnaire. Inclusion criteria were diagnosis of fibromyalgia, residing in Australia, and ≥18 years old. Participants were excluded if they did not meet the inclusion criteria. A total of n = 185 participants consented to start the questionnaire. A small proportion of participants did not meet the inclusion criteria (did not have fibromyalgia, n = 5; did not live in Australia, n = 13), and a small number failed to complete the demographic section (n = 5), leaving a total of n = 162 included for analysis. As participants progressed through the questionnaire, there were sequential dropouts, with n = 129 respondents completing the final question regarding incidental exercise (Figure 2-1). For the purposes of maximising the sample size for each question, all complete responses are included regardless of whether a respondent completed the entire questionnaire. Ethical approval was obtained by the Victoria University Human Research Ethics Committee (HRE20-095).

Demographic data was captured with single answer discrete questions. Subsequent questions captured data sequentially on fibromyalgia symptoms, medically prescribed and non-medically prescribed use of medications and the associated satisfaction scores, and dietary and exercise behaviours (Chapter 6: Appendix Qualtrics Survey Extract). This chapter discusses the finding of fibromyalgia symptoms, medication use and satisfaction.

Results

Demographic Characteristics

Females comprised almost all of respondents initiating the questionnaire (female, n = 154; male, n = 6; other, n = 2). The age categories selected by respondents were: 18-24 yr 8%, 25-34 yr 17% , 35-44

yr 21% , 45-54 yr 31%, 55-64 yr 15% , 65-74 yr 7% and, 75+ yr, 1%. The mean age of reported fibromyalgia diagnosis was 33 yr (Standard Deviation (SD) 12.3 yr). Australian state of residence reported was Victoria (n = 69), New South Wales (n = 29), Queensland (n = 29), Western Australia (n = 22), South Australia (n = 6), Tasmania (n = 4) and Australian Capital Territory (n = 2).

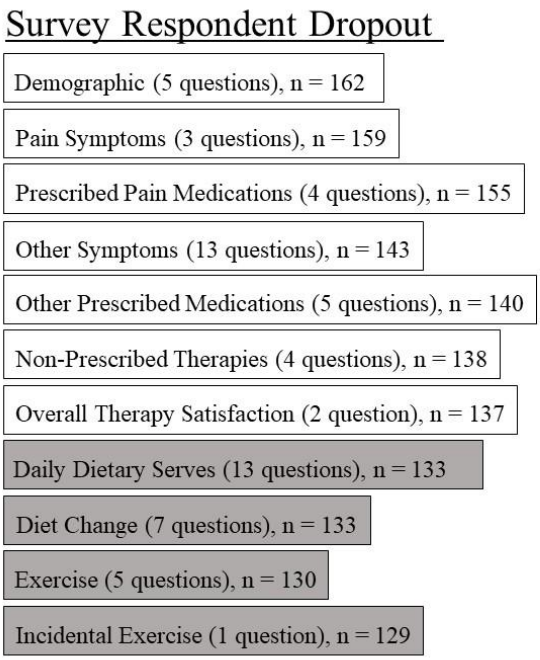


Figure 2-1. Survey respondent dropout. Numerical values indicate the number of respondents completing all questions in the relevant section of the survey.

Symptomatic Characteristics

Symptoms of pain reported by respondents included muscle ache (100%), widespread pain (96%), flare-ups (96%), headache (84%), and muscle cramps (82%) (Figure 2-2). Other notable fibromyalgia symptoms included depression (74%), suicidal thoughts (39%) and thoughts of self-harm (32%). Respondents (n = 157) reported experiencing pain on average seven days a week (67.1%), 5-6 days a week (18.4%) and three days a week or less (13.9%) in the past six months. Respondents reported comorbidities (n = 155), irritable bowel syndrome (IBS) (75%), temporomandibular dysfunction (37%) and pelvic floor dysfunction (31%), 42% reported one comorbidity, 38% reported two, and 20% reported three comorbidities. Furthermore, 27% of respondents reported experiencing other comorbidities which included costochondritis, earache, tinnitus, restless leg syndrome, ankylosis spondylitis, painful menstruation, food intolerances, post-traumatic stress disorder, rheumatoid arthritis, osteoarthritis, incontinence, torticollis, gastritis, lower back pain, bursitis, tendonitis, tachycardia and Scheuermann's kyphosis.

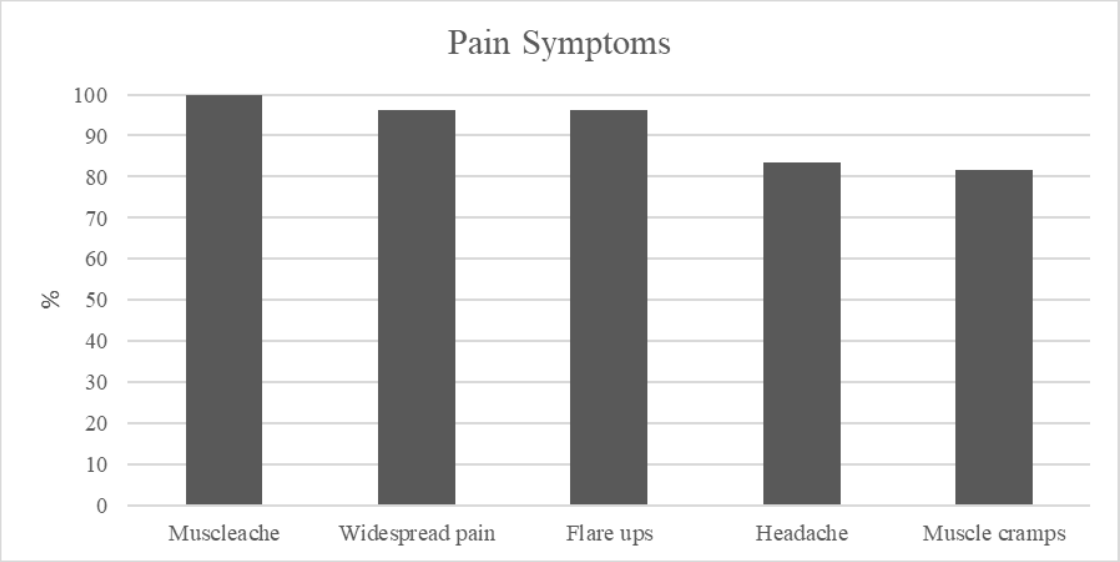


Figure 2-2. Pain symptoms reported by respondents. Data are expressed as a percentage of total respondents (%), n = 159.

Medication Characteristics

Respondents reported medications prescribed for symptoms of pain; paracetamol (66%), amitriptyline (59%), duloxetine (39%), pregabalin (31%), tramadol (30%), oxycodone (25%), PEA (12%), Tapentadol (9%), cannabidiol (8%), medicinal cannabis (6%), oroxine (6%) and milnacipran (1%) (Figure 2-3). Other medications (59%) included codeine, meloxicam (NSAIDs), hydroxychloroquine, gabapentin, targin, naltrexone, serotonin-norepinephrine reuptake inhibitors, buprenorphine patches, corticosteroids (florinef), benzocycloheptene-based drugs, armodafinil, hydromorphone hydrochloride (jurnista), Botox and topiramate.

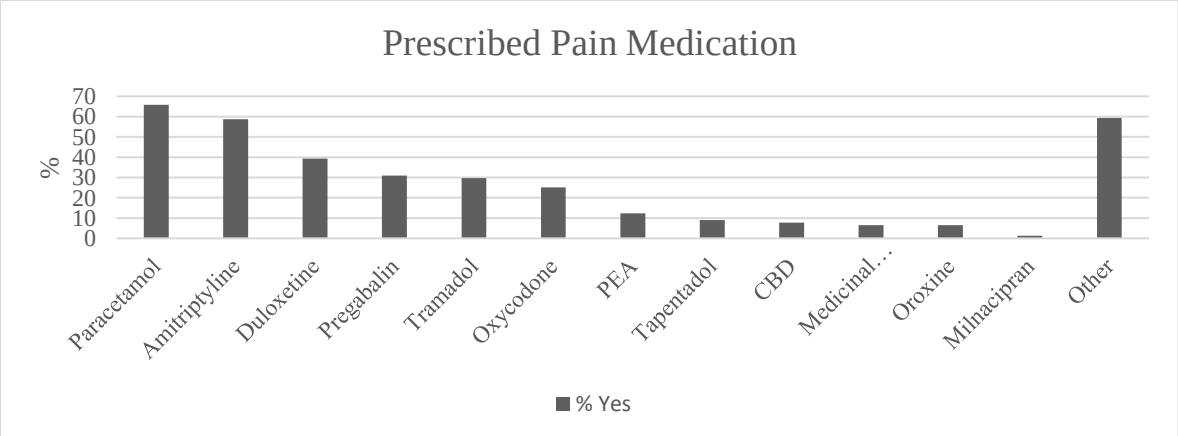


Figure 2-3. Pain medications prescribed to respondents for fibromyalgia pain. Data represented as a percentage of respondents (%), n=155. Abbreviations; Cannabidiol (CBD), Palmitoylethanolamide (PEA).

Durations of pain medication use varied among the participants. Of the participants that reported the use of a particular medication, those that reported using this pain medications for longer than two years included paracetamol 73.5%, (n = 72), amitriptyline 23.2%, (n = 29), oxycodone 65.8%, (n = 25), duloxetine 46.7%, (n = 28), oroxine 100%, (n = 10), pregabalin 36.2%, (n = 17) and other 48.9%, (n = 43). There was a high level of variation in reported duration of use of CBD, PEA, and medicinal cannabis. However, no respondents reported use of CBD and PEA for longer than two years (all data presented as a percentage of total respondents who selected individual medications) (Table 2-1).

Length of Pain Medication Use													
Duration	**Paracetamol**	**Amitriptyline**	**CBD**	**Duloxetine**	**Medicinal Cannabis**	**Milnacipran**	**Oroxine**	**Oxycodone**	**PEA**	**Pregabalin**	**Tapentadol**	**Tramadol**	**Other**
Less than 1 month	6 (6.1%)	19 (21.1%)	2 (16.7%)	11 (18.3%)	3 (30%)	1 (50%)	0	2 (5.3%)	3 (16.7%)	10 (21.3%)	5 (35.7%)	15 (34.1%)	10 (11.4%)
1-3 months	2 (2%)	13 (14.4%)	2 (16.7%)	3 (5%)	3 (30%)	0	0	4 (10.5%)	6 (33.3%)	6 (12.8%)	1 (7.1%)	9 (20.5%)	9 (10.2%)
4-5 months	1 (1%)	6 (6.7%)	2 (16.7%)	5 (8.3%)	1 (10%)	0	0	1 (2.6%)	1 (5.6%)	5 (10.6%)	0	3 (6.8%)	5 (5.7%)
6-12 months	2 (2%)	9 (10%)	4 (33.3%)	8 (13.3%)	2 (20%)	0	0	3 (7.9%)	4 (22.2%)	3 (6.4%)	3 (21.4%)	2 (4.5%)	8 (9.1%)
1-2 Years	15 (15.3%)	14 (15.6%)	2 (16.7%)	5 (8.3%)	0	0	0	3 (7.9%)	4 (22.2%)	6 (12.8%)	1 (7.1%)	4 (9.1%)	13 (14.8%)
2 years +	72 (73.5%)	29 (32.2%)	0	28 (46.7%)	1 (10%)	1 (50%)	10 (100%)	25 (65.8%)	0	17 (36.2%)	4 (28.6%)	11 (25%)	43 (48.9%)
Total n=	98	90	12	60	10	2	10	38	18	47	14	44	88

Table 2-1. Duration of pain medications reported by respondents. Data presented indicate the number of responses and the percentage of total respondents taking each medication. Respondents answered more than once, with n = 147 for this question. CBD, cannabidiol.

Respondents reported their pain symptoms after taking their pain medication. Pain was reported on a scale with five rating options: no pain 3%, (n = 4); low level mild pain 9%, (n = 13); moderate pain 59%, (n = 87); distressing pain 29%, (n = 42); and extreme pain 1%, (n = 1). The average number of medications reported per respondent were pain medications 3.3 ± SD 2.1, and non-prescribed alternative medications 3.5 ± SD 2.9 (Figure 2-7).

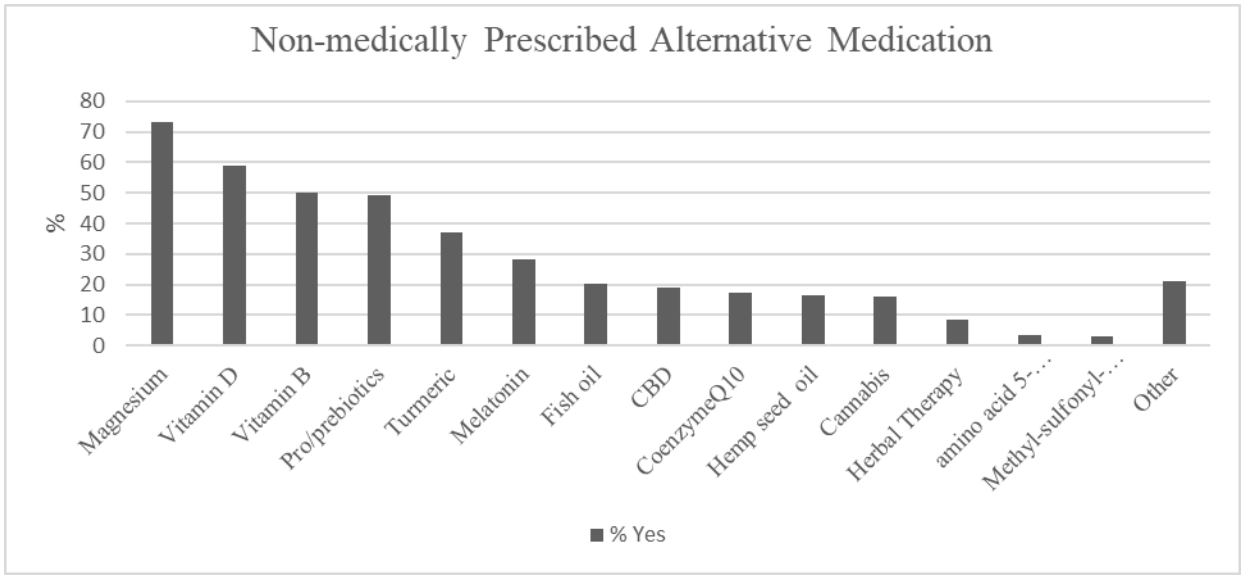


Figure 2-4. Non-medically prescribed alternative medications used by respondents. Data presented are the percentage of respondents (%), n = 138. CoQ10, co-enzyme Q10; CBD, cannabidiol; MSM, methyl-sulfonyl-methane; 5-HTP, amino acid 5-hydroxytryptophan.

Self-rated pain following non-prescribed cannabis sativa use was reported as; no pain 14%, (n = 3), low level pain 27%, (n = 6), moderate pain 18%, (n = 4), distracting pain 18%, (n = 4) and distressing pain 5%, (n = 1) (Figure 2-5). Of those participants using non-prescribed cannabis sativa and CBD oil, the length of time they were taking these were reported as; less than 1 month 18%, (n = 4), 1-3 months 18%, (n = 4), 4-5 months 5%, (n = 1), 1-2 years 9%, (n = 2) and 2 years plus 50%, (n = 11).

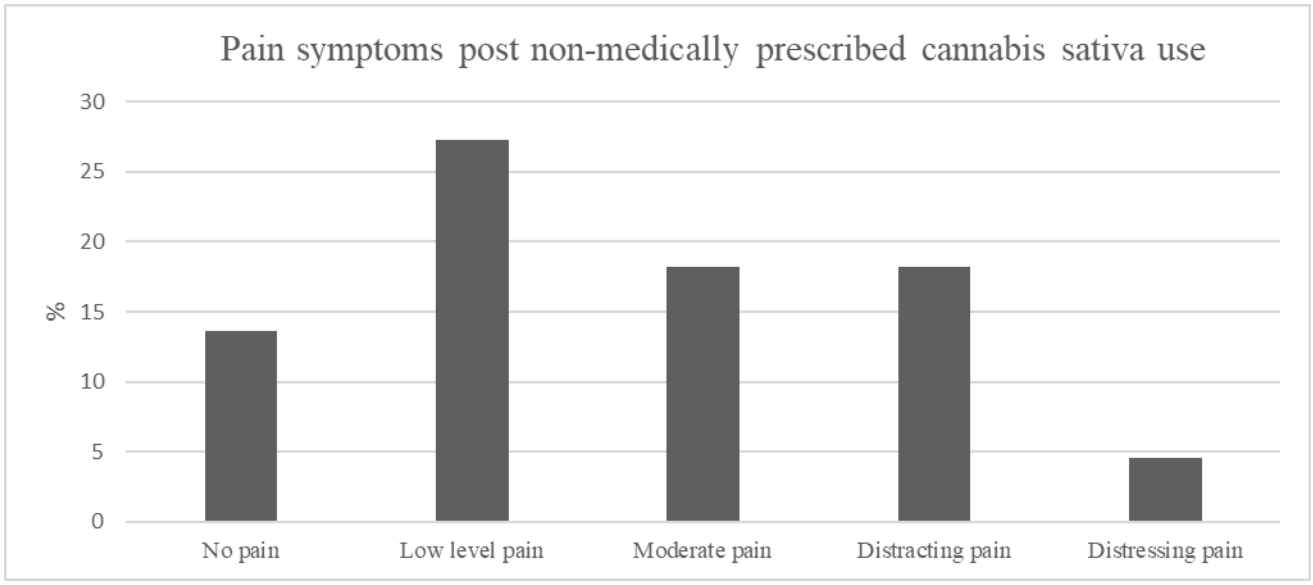


Figure 2-5. Pain symptoms post non-medically prescribed cannabis sativa use. Data presented are the percentage of respondents (%), n = 18.

Alternative non-prescribed therapy and prescribed medication satisfaction ratings were reported as; dissatisfied 27%, (n = 37), somewhat dissatisfied 27%, (n = 37), neutral 20%, (n = 27), somewhat satisfied 22%, (n = 30), and satisfied 4%, (n = 4) (Figure 2-6).

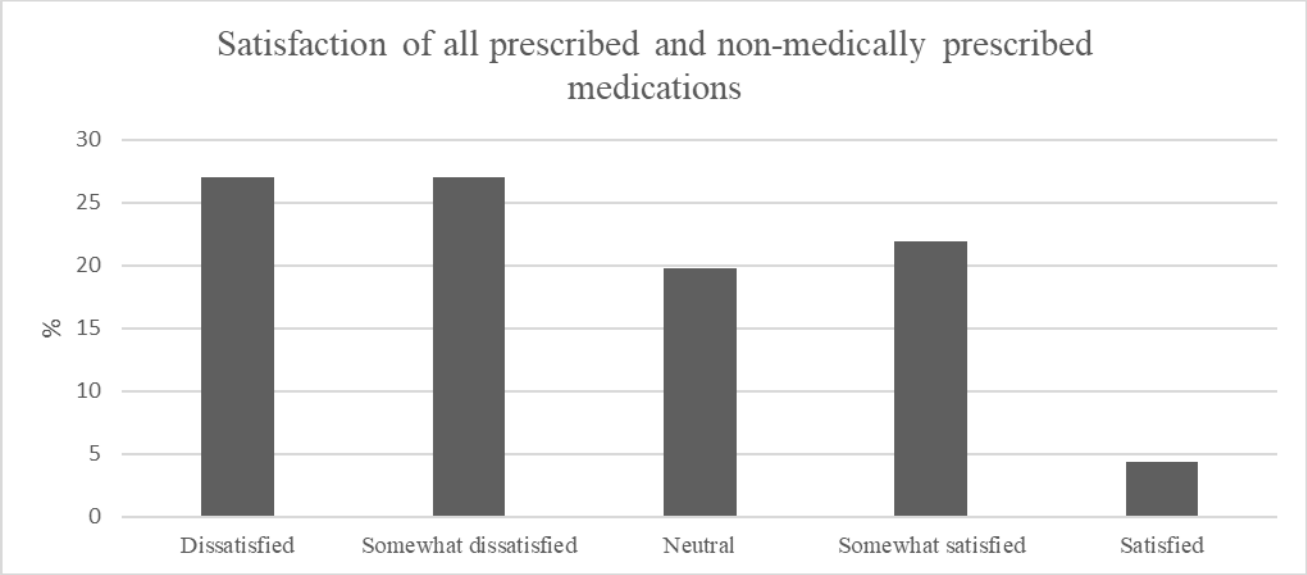


Figure 2-6. Satisfaction rating of all medications. Data presented are the percentage of respondents, n = 137.

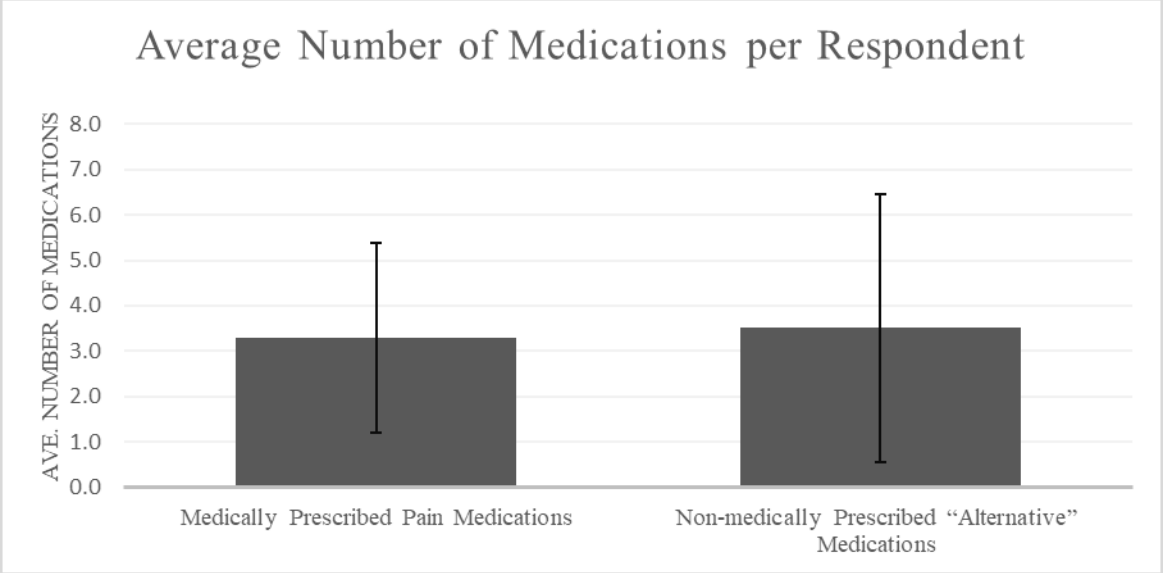


Figure 2-7. Number of medications prescribed and non-prescribed for each respondent. Data presented are the number of medications (pain, non-prescribed). Pain, n = 155; and non-medically prescribed alternative medications, n = 135. Data is reported as Means ± SD, Average (AVE.).

Discussion

Fibromyalgia is a complex medical condition with sufferers experiencing significant pain symptoms; however, the effectiveness of current pain management strategies is unclear (Kia & Choy, 2017). While an investigation into medication use and satisfaction of pain medications in people with fibromyalgia has previously been conducted in Spain (Rico-Villademoros et al., 2020), to our knowledge, there is no comparable research in an Australian population. This investigation used an online survey to sample an Australian fibromyalgia population on their prescribed and non-medically prescribed medications and associated satisfaction with pain medications. Our sample of Australian respondents with fibromyalgia reported prolonged, frequent pain symptoms and an overall lack of satisfaction, despite taking multiple pain medications. This is comparable with the (Rico-Villademoros et al., 2020) study, which found similar responses to pain experienced and medications used in participants who were diagnosed with fibromyalgia. Another notable finding was the proportion of those using non-prescribed alternative therapies.

A high proportion of respondents within the current study reported pain symptoms of muscle aches 100%, widespread pain 96%, flare-ups 96%, which agrees with findings of previous fibromyalgia studies (Andres-Rodriguez et al., 2019; Wolfe et al., 2018). An interesting finding was that a high proportion of participants reported psychological symptoms depression 74% (n = 110), suicidal thoughts 39% (n = 57) and, thoughts of self-harm 32% (n = 47). Similar findings, albeit with lower scores compared to the current study, are reported in a cross-sectional study by Ordóñez-Carrasco et al. (2020), who identified suicidal risk by accumulated scores of psychological scales (Fibromyalgia Impact Questionnaire-Revised, Beck Depression Inventory version II, Plutchik Suicide Risk scale, Interpersonal Needs Questionnaire, Defeat scale, Entrapment scale, Psychache scale and the Beck Hopelessness scale) in 54.3% (n = 82) of a Spanish fibromyalgia cohort. To further understand this risk in Australian fibromyalgia sufferers, more detailed data on psychological symptoms is needed.

The current study reported the average pain frequency of the last six months, which was reported to be seven days a week by 67% of respondents. This sample of data from the Australian population with fibromyalgia suggests that a substantial proportion of people are on long-term pain medications but have poor management of the extent of their pain, with 89% reported to experience moderate to distressing pain after taking their prescribed medication. When first-line treatment (physical therapy, cognitive behavioural therapy) fails to provide relief for these individuals, international fibromyalgia committees AWMF, EULAR and CFCG recommend prescription of pharmacotherapies to aid in the management of pain (Kia & Choy, 2017). The EULAR had the most comprehensive analysis for the efficacy of pain recommendations for fibromyalgia, and despite this recommendation, the analysis lacked high-quality studies indicating further research is required (Kia & Choy, 2017). A combination of pain pharmacotherapies is recommended by these committees for severe pain, and is observed in

the current study, however the combination of these therapies and mechanisms of action are not completely understood for the treatment of nociplastic pain, fibromyalgia symptoms and comorbidities (Kia & Choy, 2017).

On average, respondents from the current study were prescribed > 3 pain medications. The main prescribed pain medications were paracetamol (66%), amitriptyline (59%), duloxetine (39%), pregabalin (31%) and tramadol (30%). Recently, Kia and Choy (2017) noted that there is a lack of evidence of effective pain relief from many pain medications in several clinical conditions, including fibromyalgia. Paracetamol is a first-line analgesic available over the counter within Australia (Kia & Choy, 2017). Paracetamol is shown to be an effective anti-inflammatory (Bisaglia et al., 2002) and is effective for fibromyalgia pain when used in combination with tramadol (Bennett et al., 2003).The use of paracetamol in combination with duloxetine and pregabalin for the use of severe pain has been recommended by the EULAR committee guidelines, yet Kia and Choy (2017) acknowledged the lack of quality evidence for this combination.

In a comparative study to the current research, Rico-Villademoros et al. (2020) noted that 46% (n=915) of sampled Spanish fibromyalgia patients reported being prescribed two or more pharmacological treatments. The target of these pharmacological treatments was not discussed by the authors, although it was noted that 56% of respondents were prescribed medication by a rheumatologist and 20% by a pain specialist, suggesting that these medications are prescribed for fibromyalgia pain symptoms (Rico-Villademoros et al., 2020). In the Spanish cohort, the most prescribed medications were tramadol (40%), benzodiazepine (30%), duloxetine (20%) and pregabalin (19%) (Rico-Villademoros et al., 2020). Within the current study, 30% of respondents reported being prescribed tramadol for pain, 31% reported being prescribed pregabalin for pain, and 39% reported being prescribed duloxetine for pain. Benzothiazepines were not reported to be prescribed for pain in the current study, but for psychological/cognitive symptoms benzothiazepines were reported to be used by 10% of respondents (data not shown). Paracetamol was reported to be prescribed to 10.2% of Rico-Villademoros et al. (2020) respondents', whereas 66% of respondents from the current study were prescribed paracetamol for pain. The high use of multiple medications increases the likelihood of adverse side effects, and there may be a higher risk of these effects for the respondents from the current study as more reported paracetamol prescription in combination with other therapies. Although, given the complex nature of fibromyalgia it is unsurprising that pain relief from one drug alone may be insufficient (Thorpe et al., 2018). These responses, however, were self-reported by participants as medically prescribed for pain, and a major limitation of this study was that it is unclear what fibromyalgia symptoms these medications are prescribed for.
The current study also collected participant self-reports of satisfaction of their pain medication, prescribed or non-medically prescribed therapies.

After taking their prescribed medications, more than half (54%) of respondents reported being dissatisfied to somewhat dissatisfied. Additionally, most respondents reported being on their prescribed medication for more than two years. This result does not align with pharmacotherapy guidelines, whereby pharmacotherapy treatment is recommended to be ongoing only if patient benefits are sustained (Kia & Choy, 2017). Low satisfactions scores in relation to prescribed pharmacotherapies was also reported by Rico-Villademoros et al. (2020), with satisfaction scores less than 4 out of a scale of 1 – 10 numeric rating scores (NRS). Rico-Villademoros et al. (2020) also reported that the combination of pharmacotherapies did not improve satisfaction NRS scores, 1 drug (3.92 NRS) compared to > 4 drugs (4.19 NRS). Using ineffective medications for long durations may be unsafe, and the lack of satisfaction reported for prescribed medications may provide insight into why the current cohort reported using alternative, non-prescribed medications.

The use of non-medically prescribed alternative therapies was reported for the management of fibromyalgia symptoms by all respondents. On average, respondents were using > 3 non- medically prescribed medications in addition to their > 3 prescribed medications. The most popular non-medically prescribed therapies reported by respondents were magnesium (73%), vitamin D (59%), vitamin B (50%), and pro/prebiotics (49%). Comparatively, Rico-Villademoros et al. (2020) found that their Spanish cohort took similar nutritional supplements, but the proportion of respondents taking these alternatives was much lower (magnesium, 19.3%; vitamin D, 8.3%; and complex B vitamins, 7.4%) than our Australian respondents. However, there were similar satisfaction scores of prescribed therapies reported for both fibromyalgia cohorts. More research into why Australians with fibromyalgia choose to use the amount of medications they report and how that differs from Australians who are a similar age, sex and weight without fibromyalgia is needed to understand whether this rate of medication use is for symptoms management or whether it is a cultural norm. Another non- medically prescribed therapy reported to be used by 34% of respondents within the current study was prescribed cannabis sativa.

Cannabis sativa is a highly regulated pharmacotherapy in Australia, which can have pain relief and anti-anxiolytic properties (Cohen et al., 2019). Compared to 34% of respondents using non-prescribed cannabis sativa, only 13% reported being medically prescribed cannabis products (CBD 7% and medicinal cannabis 6%). Cannabis sativa was reported to be used for a varied number of symptoms including pain (82%), psychological and sensory symptoms (41%) and neuromuscular symptoms (55%) (data not shown) in the current study. Respondents who use medically prescribed medicinal cannabis (including CBD) reported having only used the medication for up to 12 months (53%). Comparatively, 50% of those using non-prescribed cannabis reported to have used for more than two years and reported improvements in pain reduction post-taking cannabis (14%, no pain) compared to pain after taking prescribed pain medication (3%, no pain). Medicinal cannabis use is also reported in

an Australian survey to improve symptoms of sleep quality (31.3%), anxiety (44%) and depression (29.5%) in respondents with chronic pain conditions (Lintzeris et al., 2020).

Cannabis sativa plant compounds have different effects, therefore those using the whole plant compared to those receiving prescribed cannabis in isolated extracts will have different drug experiences (Cohen et al., 2019). For instance, an isolated extract of the cannabis plant is THC which has analgesic effects (Berdyshev et al., 1997; Turner et al., 2020). However, excess levels of THC can be toxic and produce adverse effects such as paranoia, insomnia, tachycardia, and hypotension (Turner et al., 2020). Those suffering from fibromyalgia who use and experience less pain from using non-prescribed cannabis sativa may be gaining benefit from the analgesic effects of THC. However, this group may also be placing themselves at risk of adverse side effects (Turner et al., 2020). Furthermore, it is unknown how the patients in the current study take their cannabis, for instance whether it is via smoking, oral consumption or via some other means The route of cannabis delivery and type of cannabis used could reduce the efficacy of the medication and of other medications taken for pain relief (Bock et al., 1994).

Effective pharmacotherapies for fibromyalgia associated pain symptoms are poorly understood. This study identified a number of medically prescribed medications, with varying mechanisms of actions, and it is unclear what symptom each drug is prescribed for. Pain medications currently prescribed for fibromyalgia provide inadequate relief; however, a substantial proportion of respondents are using non-medically prescribed cannabis sativa, which might indicate poorly managed pain from conventional pharmacotherapies, or poor lifestyle choices that reduce the effectiveness of medically prescribed therapies. Currently, there is little research for cannabis sativa and its derivatives efficacy on fibromyalgia symptoms and the addition of combination therapies. Further research is also needed on prescribed pharmacotherapy dosages and relevant interprofessional practitioners that are used as part of a treatment plan for fibromyalgia patients.

The current study initiated the investigation into pain management for fibromyalgia in Australia using online survey methods and convenience sampling during the COVID-19 pandemic; however, this study faced some limitations. Despite the high use of dietary supplements (excluding cannabis sativa) from the current study, it was unclear as to whether this cohort use these supplements to treat their fibromyalgia pain symptoms. Pain scales regarding medically prescribed and non-medically prescribed medications were also limited as numerical rating scales were not uniform in this study. Limitations in social media distribution algorithms meant that this study used convenience sampling to collect data rather than representative sampling, which could increase participation bias and therefore impact outcome validity (Andrade, 2020). For example, this study may not represent the Australian population with fibromyalgia accurately, over 50% of respondents from the current study

reported to be aged between 35-54 years, this age range may by the most common age to be using social media forums. It is likely that this survey has underrepresented patients who are older, and who have more severe symptoms, who were unable to access the study. Therefore, these findings may not be able to be generalised to the broader Australian fibromyalgia population.

Conclusion

Those diagnosed with fibromyalgia in Australia are frequently prescribed more than three different pain medications and are also taking more than three different non-prescribed medications/supplements for the management of their symptoms. This cohort reported being moderately to largely dissatisfied with their prescribed pain medications due to reports of frequent pain symptoms daily after using their pain medication. Non-prescribed cannabis sativa was also reported to be used as an alternative therapy. More research is required to understand the therapeutic value of prescribed and non-prescribed pharmacotherapies for the symptoms of pain and the impact that the treatment management plan has on pain severity and the mental health of those with fibromyalgia in Australia.

3. Chapter Three: Lifestyle and Dietary Choices of Australians with Fibromyalgia

Abstract

Background:

Fibromyalgia is a syndrome whereby symptoms of pain, fatigue, and anxiety, and comorbidities such as irritable bowel syndrome, reduce quality of life. Lifestyle factors such as exercise, diet, and nutritional supplementation may modify the severity of fibromyalgia symptoms. However, there is a lack of research into lifestyle factors in the Australian fibromyalgia population. The aim of this study was, therefore, to capture the lifestyle habits of Australians with fibromyalgia.

Methods:

An observational, cross-sectional online questionnaire was conducted in Australia from August to September 2020. The questionnaire was distributed via social media forums and a Victorian pain clinic and comprised questions regarding physical activity and dietary habits.

Results:

Most respondents, 81% (n = 82), reported exercising, short walks being the preferred exercise modality (70%). Resistance exercise training was reported by 31%. Low exercise intensity (mean Borg Rate of Perceived Exertion 2.8 ± SD 1.57) and exercise durations of 15-30 minutes was reported by 55%. Incidental exercise for ten minutes or longer, three or more times each week, was reported by 37% (n = 48) of respondents. Only a small number of respondents met Australian dietary guidelines; for vegetables, 22% ate ≥ five serves·day^{-1}; for fruit, 29% ate ≥ two serves·day^{-1}; for grains and cereals, 2.3% ate ≥ six serves·day^{-1}; for lean meats and alternatives, 78% ate ≥ two serves·day^{-1}; for dairy and alternatives, 53% ate ≥ two serves·day^{-1}; and for discretionary items, 82% ate ≤ two serves·day^{-1}. Most respondents (76%) reported changing their diet to manage their fibromyalgia symptoms. The proportion of respondents who had tried diet change for symptom management and reported that change being helpful for their symptoms was: low sugar, 32% (n = 43), gluten free 31% (n = 41), no alcohol 29% (n = 38), reduced red meat 17% (n = 23). Respondents also reported those diets not helpful for symptoms: low sugar 29% (n = 38), no alcohol 29% (n = 38), reduced red meat 27% (n = 36), low fat 26% (n = 35), gluten free 18% (n = 24). Respondents typically adhered to a diet, helpful or not, for three months or more 71% (n = 52), however only 25% (n = 26) reported still using a diet that they found helpful for symptom management. The main dietary fats reported to be consumed regularly by respondents were extra virgin olive oil 79% (n = 108) and animal butter 61% (n = 83).

Conclusion:

This questionnaire of Australians with fibromyalgia found that most respondents did not meet Australian physical activity and dietary recommendations to maintain health. Those who exercised regularly reported low exercise intensities, and less than a third undertook resistance exercise. Many respondents reported trialling different diets for the management of their fibromyalgia symptoms, however, a similar number of participants reported these diets as not helpful as those that indicated that they were helpful in the management of their symptoms. More research is required to identify why Australians with fibromyalgia undertake low levels and intensities of physical activity and to understand whether certain dietary changes impact symptom severity.

Introduction

Fibromyalgia is a syndrome comprising symptoms of widespread pain, fatigue, depression, and anxiety (Vincent et al., 2013). Fibromyalgia is frequently associated with comorbidities such as irritable bowel syndrome, systemic lupus erythematosus and obesity (Bennett et al., 2007). Development of fibromyalgia is highly varied, and it affects approximately 2-5% of the population (Wolfe et al., 2018). The underlying pathophysiology of the condition is complex which can be problematic for sufferers attempting to relieve symptoms via pharmaceutical interventions, and for the prescription of certain therapies as there is a lack of high-quality evidence for the effectiveness of pharmacotherapy combinations (Kia & Choy, 2017). Furthermore, low levels of satisfaction have been reported for combination pharmacotherapy in fibromyalgia cohorts in Spain (Rico-Villademoros et al., 2020) and in Australia (thesis chapter two), suggestive of the challenges in managing fibromyalgia signs and symptoms with pharmacotherapies alone.

Review of the guidelines for the management of fibromyalgia shows that non-pharmacological therapies (e.g., physical activity) are encouraged as a first-line treatment (Kia & Choy, 2017). Synthesised findings demonstrate that physical activity is effective for improving a range of outcome measures in this population, including pain (Sosa-Reina et al., 2017). In their systematic review and meta-analysis of therapeutic exercise studies in people with fibromyalgia, Sosa-Reina et al. (2017) found that the combination of aerobic and resistance exercise reduced pain (standard mean difference (SMD): -1.11, 95% CI: −1.52 to −0.71), depression (SMD: -0.40, 95% CI: −0.55 to −0.24), and fibromyalgia disease severity scores (ES 95% CI: −0.89 to −0.45), and increased physical (SMD: 0.77, 95% CI: 0.47 to 1.08) and mental (SMD: 0.39, 95% CI: 0.52 to 0.27) quality of life scores. In Australia, there are no specific physical activity guidelines for fibromyalgia; physical activity guidelines for adults aged 18-65 years are provided by the Federal Government Department of Health and recommend 150-300 minutes per week of moderate intensity physical activity or 75-150 minutes per week of vigorous intensity activity (or a combination of both), with at least two sessions per week of resistance-type exercise (Department of Health, 2021). However, it is unknown whether the Australian fibromyalgia population meet these guidelines.

The National Health and Medical Research Council developed evidence-based dietary guidelines for healthy eating in Australia (Department of Health, 2020). These guidelines recommend eating a varied diet with daily inclusion of lean meats (or alternatives), vegetables, dairy (or alternatives), grains and cereals, and fruits, and limiting intake of discretionary high fat and high sugar food products (Department of Health, 2020). It is unknown whether the Australian fibromyalgia population eat according to these guidelines.

Alternative dietary approaches to the Australian guidelines may benefit some individuals' signs and symptoms of fibromyalgia and associated comorbidities. For instance, the low fermentable oligo-, di-, mono-saccharides and polyol (FODMAP) diet has shown promise for reducing symptoms of irritable bowel syndrome, a painful fibromyalgia comorbidity (Schumann et al., 2018). In their meta-analysis of nine studies totalling 596 participants, Schumann et al. (2018) found that in individuals with irritable bowel syndrome, the low FODMAP diet improved gastrointestinal symptoms (SMD: -0.62, 95% CI: -0.93 to -0.31), abdominal pain (SMD: -0.50, 95% CI: -0.77 to -0.22), and health-related quality of life scores (SMD: 0.36, 95% CI: 0.10 to 0.62) compared to other diets. Obesity is another common comorbidity of fibromyalgia that is correlated, albeit generally weakly (correlation ES $\leq$ 0.39) and not in all meta-analysed studies, with higher scores of pain severity, depression, and fatigue (D'Onghia et al., 2021). In addition, diet-induced weight loss has been shown to reduce the severity of fibromyalgia symptoms. In a randomised controlled trial of 83 obese individuals with fibromyalgia, 41 participants completed a six month trial of a hypocaloric, body-weight reduction diet of ~ 5021 kilojoules/day (15–20% protein, 50–55% carbohydrates, and ~ 30% fat) and reduced their body mass index by 3.27 $kg \cdot m^{-2}$ (32.3 ± 1.4, 95% CI: 2.69 to 3.85) and reported lower scores on the fibromyalgia impact questionnaire (47 ± 5.7, 95% CI: 1.33 to 7.95) compared to the weight stable control group (Senna et al., 2012). Intake of dietary fat is associated with obesity (Alvheim et al., 2012), and yet, a higher ratio of omega 3 (n-3) to omega 6 (n-6) fatty acid intake may benefit fibromyalgia symptoms, comorbid with systemic lupus erythematosus (Charoenwoodhipong et al., 2020). There is no available data on the dietary habits of Australians with fibromyalgia, nor the fat distribution in their diets.

To date, it is unknown whether the Australian fibromyalgia population exercise regularly, eat a balanced diet or whether they modify their diet to manage their fibromyalgia symptoms. This study aimed to gain insights into the physical activity levels and dietary habits of Australians with fibromyalgia.

Methods

An observational, cross-sectional study comprising an online questionnaire (Qualtrics) was conducted in Australia from August 2020 to September 2020. A link to the online questionnaire was distributed via social media forums and a local pain clinic. Participants completed screening questions to assess eligibility to undertake the questionnaire. Inclusion criteria were diagnosis of fibromyalgia, residing in Australia, and over 18 years old. Subsequent questions gathered information about participant demographic, fibromyalgia symptoms, medication use and satisfaction, and exercise and dietary habits (Figure 3-1). This chapter discusses the finding of the exercise and dietary habits questions. A total of n = 185 participants consented to starting the questionnaire. A small proportion of participants did not meet the inclusion criteria (did not have fibromyalgia, n = 5; did not live in Australia, n = 13) and a small number failed to complete the demographic section (n = 5), leaving a total of n = 162 included for analysis. As participants progressed through the questionnaire, there were sequential

dropouts, with n = 129 respondents completing the final question regarding incidental exercise (Figure 3-1). For the purposes of maximising the sample size for each question, all complete responses are included regardless of whether a respondent completed the full questionnaire. Ethical approval was obtained by the Victoria University Human Research Ethics Committee (HRE20-095).

Demographic data was captured with single answer discrete questions. Subsequent questions captured data sequentially on dietary fats, diet changes that were perceived to aid or hinder fibromyalgia symptoms, exercise habits, exercise intensity and session duration, and incidental exercise (Chapter 6: Appendix Qualtrics Survey Extract). Questions regarding the average daily consumption of major food groups were developed based on The Australian Guide to Healthy Eating (Department of Health, 2020). Questions relating to exercise modes were developed based on the Borg Rating of Perceived Exertion (RPE) exercise intensity scale (Norton et al., 2010) and the Department of Health physical activity and exercise guidelines for adult Australians ages 18 to 64 years (Department of Health, 2021).

Results

Females comprised almost all of respondents initiating the questionnaire (female, n = 154; male, n = 6; other, n = 2). The age categories selected by respondents were: 18-24 yr, 8% (n = 13); 25-34 yr, 17% (n = 27); 35-44 yr, 21% (n = 34); 45-54 yr, 31% (n = 51); 55-64 yr, 15% (n = 25); 65-74 yr, 7% (n = 11) and 75+ yr, 1% (n = 1). The mean age of reported fibromyalgia diagnosis was 33 yr (Standard Deviation (SD) 12.3 yr). Australian state of residence reported by respondents was Victoria (n = 69), New South Wales (n = 29), Queensland (n = 29), Western Australia (n = 22), South Australia (n = 6), Tasmania (n = 4) and Australian Capital Territory (n = 2).

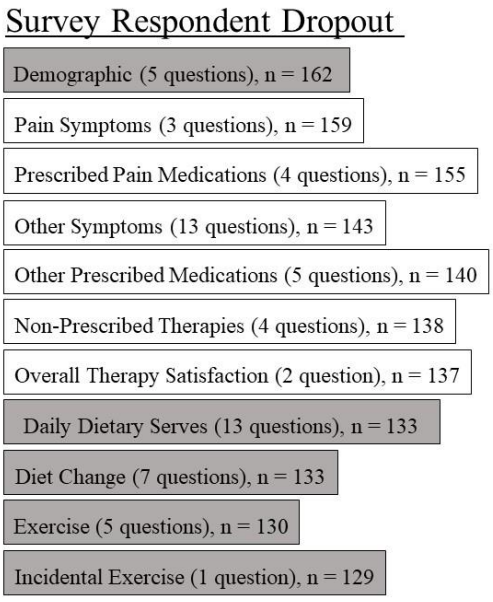


Figure 3-1. Questionnaire respondent dropouts across the questionnaire sections. Data presented are the question section, number of questions, and number of respondents who completed that section. Questionnaire sections shaded grey represent those included in the current chapter; earlier questionnaire sections are reported in Chapter 2.

Comorbidities were reported by n = 125 respondents (Figure 3-1). 42% reported one comorbidity, 38% reported two, and 20% reported three comorbidities. Respondents reported having irritable bowel syndrome (74.8%), temporomandibular syndrome (37.4%), and pelvic floor dysfunction (31%). 27% also reported other comorbidities, which were: costochondritis, earache, tinnitus, restless leg syndrome, ankylosis spondylitis, painful menstruation, food intolerances, post-traumatic stress disorder, rheumatoid arthritis, osteoarthritis, incontinence, torticollis, gastritis, lower back pain, bursitis, tendonitis, tachycardia and Scheuermann's kyphosis.

N = 130 respondents answered questions about exercise (Figure 3-1). 81% of respondents reported doing exercise. Respondents that reported exercising (n = 105), n = 26 participants selected 32 different responses for types of resistance exercise and, n = 104 selected 180 different responses for types of cardiovascular exercise. The most common exercise modalities were short walks, long walks and using weights at home (Table 3-1). Other modes of exercise reported by 43% of respondents were stretching, physiotherapy, dance, hydrotherapy, yoga, Pilates, vibration board, tai chi, and swimming (Table 3-1). Incidental exercise recorded by the number of times walking for ten minutes or longer was reported by respondents; one ten-minute walk (minimum) per week 39%, (n = 50); two ten-minute walks (minimum) per week 24%, (n = 31); three ten-minute walks (minimum) per week 18%, (n = 23); four ten-minute walks (minimum) per week 7%, (n = 9); five ten-minute walks (minimum) per week 1%, (n = 1); and six or more ten-minute walks (minimum) per week 12%, (n = 15).

Respondents' Exercise								
	Intensity	Light		Moderate		Vigorous		High
	n= (%)	**1**	**2**	**3**	**4**	**5**	**6**	**>7**
Cardiovascular Exercise								
Short Walks	74 (70%)	16 (22%)	11 (15%)	21 (28%)	12 (16%)	7 (9%)	3 (4%)	3 (5%)
Long Walk	33 (31%)	0	1 (3%)	11 (33%)	12 (36%)	5 (15%)	3 (9%)	1 (3%)
Cardio at home	9 (9%)	1 (11%)	0	1 (11%)	2 (22%)	2 (22%)	1 (11%)	2 (22%)
Jog/run	6 (6%)	0	0	1 (17%)	1 (17%)	1 (17%)	0	3 (50%)
Sport	2 (2%)	0	0	0	0	1 (50%)	0	1 (50%)
Cycle	11 (10%)	3 (27%)	0	0	3 (27%)	1 (9%)	2 (18%)	2 (18%)
Resistance Exercise								
Personal Trainer	6 (6%)	0	0	1 (17%)	1 (17%)	1 (17%)	2 (33%)	1 (17%)
Weights at home	14 (13%)	1 (7%)	0	4 (28%)	2 (14%)	2 (14%)	3 (21%)	2 (14%)
Gym and use the machines	5 (5%)	0	0	0	1 (20%)	2 (40%)	2 (40%)	0
Gym and go to classes	4 (4%)	0	0	0	0	0	2 (50%)	2 (50%)
Gym and use free weights	2 (2%)	0	0	0	0	0	1 (50%)	1 (50%)
Other	45 (43%)	11 (24%)	4 (9%)	11 (24%)	12 (27%)	4 (9%)	2 (4%)	1 (2%)

Table 3-1. Exercise and associated exercise intensity reported by respondents. Data are presented as the total number of respondents and as a percentage (%) of total respondents who reported to exercise (n = 105); respondents could select more than one response. Borg intensity scale used for intensity descriptors (Williams et al., 2017).

The intensity of exercise was reported according to the Borg Rate of Exertion (RPE) Scale rating (Table 3-1). The average intensity respondents reported exercising at was (Borg RPE 1-10 numerical score rating) 2.8 ± SD 1.57, which is a somewhat light intensity.

Respondents reported the average amount of time they spent exercising at their preferred intensity: 15-30 minutes, 55% (n = 58); 30-45 minutes, 32% (n = 34); 45-60 minutes, 8% (n = 8), and more than 60 minutes, 5% (n = 5). The most selected exercise duration reported by respondents was 30-45 minutes (n = 34). Weekly frequency of exercise was reported as; one day per week, 11.4% (n = 12); two days per week, 18%, n = 19; three days per week, 35%, n = 37; four days per week, 4.8%, n = 5; five days per week, 26%, n = 27; six days per week, 4.8%, n = 5.

Respondents reported their daily serves of major food groups outlined in the Australian Guide for Healthy Eating (Department of Health, 2020). The proportion of respondents who met or exceeded the dietary guidelines for each food group was then calculated. Those who reported two serves of lean meats and dairy or alternatives per day was calculated to meet the recommended two and a half serves of lean meats as the question grouped the serves as whole numbers, not half serves. The proportions were: vegetables, 21.8% ate five serves or more per day; fruit, 29.3% ate 2 serves or more per day; grains and cereals, 2.3% ate six serves or more per day; lean meats and alternatives, 78.2% ate two serves or more per day; dairy and alternatives, 52.6% ate two serves or more per day; and discretionary items, 82% ate two serves or less per day (Table 3-2).

Daily Dietary Inake reported by Respondents						
	Vegetables	**Fruit**	**Grains and Cereals**	**Lean Meats and Alt.**	**Dairy and Alt.**	**Discretionary Items**
<1 Serve	13 (9.8%)	93 (69.9%)	38 (28.6%)	27 (20.3%)	62 (46.6%)	67 (50.4%)
1-2 Serves	57 (42.9%)	35 (26.3%)	68 (51.1%)	86 (64.7%)	52 (39.1%)	42 (31.6%)
3-4 Serves	34 (25.6%)	0	23 (17.3%)	17 (12.8%)	16 (12%)	21 (15.8%)
5-6 Serves	20 (15%)	4 (3%)	2 (1.5%)	1 (0.8%)	2 (1.5%)	2 (1.5%)
7 Serves +	9 (6.8%)	0	1 (0.8%)	0	0	0
Approximate or greater than recommended (%) *discretionary items equal to or less than	21.8	29.3	2.3	78.2	52.6	82.0
Recommended serves for females						
19-50 years	5	2	6	2.5	2.5	2
51-70 years	5	2	4	2	4	2

Table 3-2. Respondents reported daily dietary intake of food group serves. Data presented as a number, n = 133 and as a percentage (%). Recommended daily serves (equal to or greater than recommended) are reported for female serves only, as most respondents reported to be female at this stage of the questionnaire (females n = 127 males n = 4, other n = 2).

Diet change was reported by respondents 76% (n = 101). Diets that respondents reported trying to manage their fibromyalgia symptoms were low sugar 81%, (n = 82); no alcohol 75%, (n = 76); gluten free 64%, (n = 65); reduced red meat 58%, (n = 59); low fat 53%, (n = 54); vegetarian 41%, (n = 41); whole food diet 38%, (n = 38); paleo diet 22%, (n = 22); Atkins low carbohydrate diet 9%, (n = 9); and other 38%, (n = 38); low FODMAPS diet, ketogenic diet, vegan and intermittent fasting. On average, each respondent reported trying (mean ± SD) 4.89 ± 1.88 diet changes for the management of their condition. Of these respondents, 49% reported diets they had tried helpful for managing their fibromyalgia symptoms (Figure 3-2).

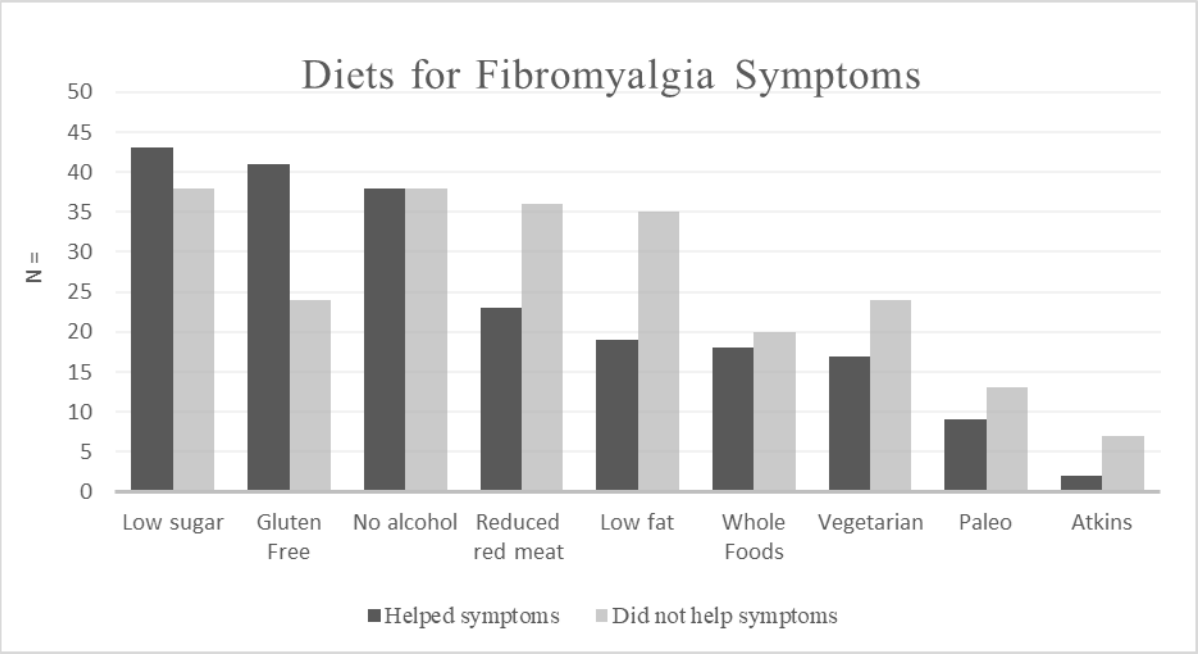


Figure 3-2. Dietary approaches reported by respondents to either help or not help fibromyalgia symptoms. Data presented as a total of respondents, n = 133, respondents reported more than one diet.

75 respondents recorded the duration of the trialled diets. Duration of adherence to the helpful diets was reported for an average of one month or less by 8%, (n = 6) of respondents, one to three months, 13%, (n = 10) and for three months or more by 40%, (n = 30) of respondents, 39%, (n = 29) selected other, which included a variety of responses including the continuing adherence to the diets. 72 respondents recorded the duration of adherence to the not helpful diets. Duration for an average of one month or less was reported by 19%, (n = 14); one to three months by 19%, (n = 14); and three months or more 31%, (n = 22) of respondents; 31%, (n = 22) reported other. Diets were reported not helpful for symptoms of irritable bowel syndrome, headaches, irritability, anxiety, muscle stiffness, nausea, and brain fog. Respondents reported to still be using the helpful diet 32%, (n = 24).

Respondents reported their daily consumption of fluids, including coffee, tea, juice, and water, as: 1-2 glasses/cups per day (~200-300 ml) was reported by 5%, (n = 6); 3-4 glasses/cups per day (~400-800 ml) was reported by 17%, (n = 20); 1-2 litres per day was reported by 54%, (n = 65); 2-3 litres per day was reported by 24%, (n = 29); and no respondent reported drinking more than 3 litres per day.

Dietary fats reported to be used by respondents (n = 137) are shown in Figure 3-3. The average number of times fats and oils were consumed over a 14-day period was extra virgin olive oil (nine times), animal butter (nine times), Nuttelex (nut spread) (nine times), margarine (seven times), flaxseed oil (six times), nut butter (five times), canola oil (five times), coconut oil (five times), ghee (five times), sunflower oil (five times), avocado oil (four times), peanut oil (three times), walnut oil (one time) and other (one time).

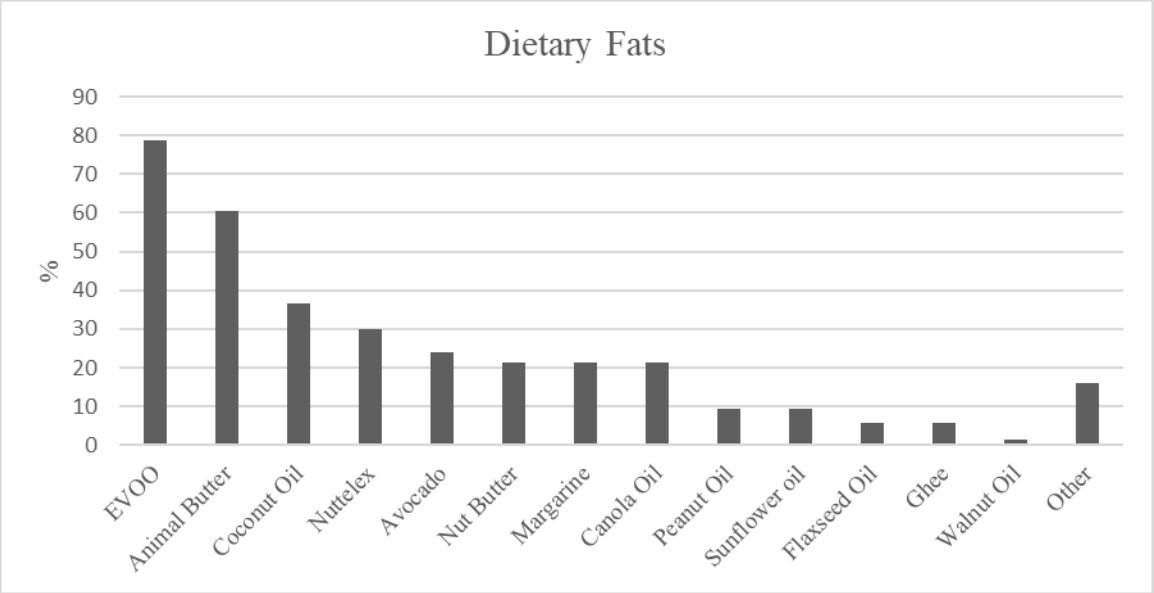


Figure 3-3. Dietary fats consumed by respondents. Data presented as a percentage of respondents (%), n = 133. EVOO, extra virgin olive oil.

Discussion

Adherence to the dietary and exercise guidelines are important for the maintenance of overall good health and quality of life (Department of Health, 2020, 2021). The aim of this study was to understand the exercise and dietary habits of a sample of the Australian fibromyalgia population. A key finding was that most of the cohort did not meet the minimum recommended exercise guidelines for Australians 18-64 years of age. Additionally, only a small number of respondents reported eating according to the Australian guide for healthy eating, and most trialed a variety of modifications to their diet to manage their symptoms. Our exercise findings are particularly important because physical activity has been shown to reduce the impact of fibromyalgia and the risk of development and severity of comorbidities (Hamaguchi et al., 2020; Larsson et al., 2015). Although dietary interventions are an emerging area of research for fibromyalgia management, there is some evidence that certain dietary

alterations reduce the overall impact of the disease (Dionne et al., 2018). Dietary exploration could suggest that this cohort are seeking better management of their fibromyalgia, yet their low exercise may indicate that they don't understand, or are unable to complete, the primary non-phamacotherapeutic treatment option.

The Australian Department of Health guidelines recommend 150-300 minutes per week at a moderate intensity (3-5/10 on the Borg RPE scale) to maintain health. Although we did not specifically ask participants how many minutes of physical exercise they did each week, based on calculated averages of days per week spent exercising reported by participants, the mean range of exercise duration was approximately 104 minutes, which is substantially less than the guidelines suggest. The mean exercise session intensity reported (2.8 / 10) was also below moderate to vigorous recommendations. Together, these data suggest that a substantial proportion of Australians with fibromyalgia may not be meeting adult physical activity recommendations. It is important to note that exercise-related questions were developed from the guidelines for Australians aged 18-64 years, which suggest moderate (2.5 to 5 hours per week) or vigorous (1.2 to 2.5 hours per week) intensity exercise, or some equivalent combination, per week (Department of Health, 2021). While five respondents to exercise questions were aged 65-74 years of age, because minimum exercise guidelines for adult and older adults are equivalent we elected to group all the responses rather than removing those of the older respondents.Walking was the most common exercise reported by our cohort. In their systematic review and meta-analysis on the outcomes of walking for pain conditions, including fibromyalgia, O'Connor et al. (2015) reported short- (< 8 weeks) and medium-term (> 2 and < 12 months) walking was associated with reduced self-reported pain (0-100 point pain scale reduction: short-term (mean difference MD): -5.31,95% CI, -8.1 to -2.4); medium-term (MD: -7.92, 95% CI: -12.4 to -3.5), and there may also be a benefit (MD: -2.22, 95% CI: -6.0 to 1.6) in the long-term (> 12 months). Similarly, self-reported functional status was also improved by short- (0-53 100 point function scale reduction: (MD:-6.47, 95% CI: -12.0 to -0.95), medium- (0-100 point function scale reduction: MD: -9.31, 95% CI: -14.0 to -4.6) and long-term (0-100 point function scale reduction: MD: -5.22, 95% CI: -7.2 to -3.2) walking. It is important to note that these meta-analysed findings by O'Connor et al. (2015) comprised n = 2,384 participants with the mean age 57 years, and 77% women; only four studies of 17 (n = 337) included people with fibromyalgia. Comparably, only 15% of the cohort in the current study are in the 55-64 years age range and 95% reported as female. Furthermore, O'Connor et al. (2015) did not describe the intensity of walking required to elicit the indicated effects. Australian physical activity guidelines recommend an exercise intensity of moderate to vigorous (Department of Health, 2021), 44% of respondents reported undertaking moderate intensities for short walks and 69% for long walks, while 18% reported vigorous to high intensity short walks and 27% for long walks. However, precise durations of short and long walks were not determined, and it is unknown whether respondents from the current study have adhered to their walking routine for short (< 8 weeks) or long

(> 2 months to 12 months) periods of time. From the available data we are unable to determine whether the volume and intensity of walking would be sufficient to provide meaningful benefit to pain or functional status in our cohort. Future research should evaluate the impact of walking dose on these measures in Australians with fibromyalgia.

Only 25% (n = 26/105) of the current cohort reported doing any form of resistance exercise. Federal guidelines recommend all adults achieve two days of moderate to vigorous strengthening exercise each week. It is possible that the majority of the current cohort do not achieve this recommendation because they primarily reported undergoing walking exercise. Additionally, only a small proportion of those undertaking resistance exercise reported working with an exercise professional (n = 6). Therefore, it is also possible that the current cohort may not know how to exercise at moderate to vigorous intensities when resistance training without professional assistance.

Overall, our data suggests that Australians with fibromyalgia have low physical activity and strengthening exercise volume and intensity. Others have indicated that individuals with fibromyalgia are at risk of muscle dysfunction and dynapenia (Kapuczinski et al., 2021). Dynapenia is a reduction in muscle strength and endurance. It may also be a precurser to sarcopenia (muscle mass loss), which can be attenuated or reversed with strength training (Sampaio et al., 2020). Strength training performed at a moderate intensity is shown to reduce self-reported pain, increase pain acceptance, and improve mental and physical health outcomes in fibromyalgia (Larsson et al., 2015). Larsson et al. (2015) used a randomised multi-centre trial comprising 67 participants for a resistance exercise group compared to 63 participants in a relaxation therapy comparative group. The resistance exercise group undertook a 15-week training regimen, and the authors attempted to manage participant exercise intensity using pre-intervention estimation of one repetition maximum (1RM) loads and a progressive loading approach (Larsson et al., 2015). While Larsson et al. (2015) reported this approach was done to avoid adverse immune responses, not all participants reached the intended 80% 1RM, and it was unclear from the reported information how progression was modified after eight weeks of training. Regardless, there were reported improvements in strength measures, for example, increases in isometric knee extension force (N·m-2) of 21% (pre-post training change: 30.4 N·m-2 ± 71.9 N·m-2), isometric elbow force of 25% (2.4 ± 3.3 N·m-2), hand grip force of 22% (20.1 ± 36.1 N·m-2), and physical health status of 10.6% (3.3 ± 7.2) (Larsson et al., 2015).Moreover, there was a reduction of pain intensity visual analogue score of 23.3% (-11.5 ± 25.1), and increases in pain acceptance of 9.0% (5.7 ± 13.1), and mental health status of 8.8% (3.3 ± 10.3) (Larsson et al., 2015). Therefore, resistance training can benefit strength and physical functions and reduce pain and mental health measures in people with fibromyalgia.

Moderate to high resistance exercise intensities are also used as a preventative intervention for those at risk of bone mineral diseases, for instance, osteopenia and osteoarthritis (Kistler-Fischbacher et al.,

2021). In their systematic review and meta-analyses, Kistler-Fischbacher et al. (2021) reported resistance exercise (alone and in combination with other forms of exercise) decreased the risk for bone fractures in postmenopausal women (mean difference (MD): 0.51, 95% CI: 0.30 to 0.88) compared to non-resistance exercise control groups. Additionally, moderate exercise intensity provides mechanical stimulus for improvements in total hip bone mineral density (MD: 0.008 g/cm², 95% CI: 0.004 to 0.012), and at the femoral neck (resistance exercise only; MD: 0.024 g/cm², 95% CI: 0.004 to 0.043). Kistler-Fischbacher et al. (2021) also reported exercise performed at a high intensity (impact and resistance training) significantly improved lumbar spine bone mineral density (MD: 0.038 g/cm², 95% CI: 0.014 to 0.062). However, the high intensity interventions had a small sample size (Kistler-Fischbacher et al., 2021). Exercise performed at a low intensity showed no significant effect on bone mineral density adaptations for postmenopausal women. A criticism of the reviewed studies was that exercise intensity ranges reported were ambiguous, there were no clear categorical inclusions for repetition ranges, exercise tempos, 1RM percentages ranges, upper or lower body exercises, or whether exercise included the use of weighted machines, free weights or barbell equipment, which all impact subjective intensity responses of exercise performed (Kistler-Fischbacher et al., 2021). Ideally, exercise protocols would include an RPE scale alongside the 1RM %, for example, the Borg RPE scale for clarity of exercise intensity and validity of exercise protocol (Williams, 2017). Altogether, this data coupled with our survey findings suggests that Australians with fibromyalgia may be at risk of conditions of low bone mineral density.

Physical activity is recommended as a first-line treatment for fibromyalgia and is successful in reducing pain, disease severity and the overall burden of the disease. Earlier (Chapter Two), we found that Australians with fibromyalgia had poorly managed pain and were taking a variety of pharmacotherapies to treat pain and other symptoms. Our group of respondents was too small to identify relationships between physical activity and pain as only two-thirds of the sample did any physical activity, and only one-quarter of those reported doing resistance exercise. It could be speculated that if physical activity levels were higher, reported frequency and intensity of pain and use of pharmacotherapies might reduce in this population. More research investigating why Australians with fibromyalgia report to undergo low intensity levels of physical activity and many not including resistance exercise in their weekly physical activity routine is warranted. More research is also needed investigating muscle and bone quality and function in this population because of a plausible increased risk of low physical activity and chronic conditions.

Only a portion of the Australians with fibromyalgia sampled reported eating habits consistent with the Australian guide for healthy eating. For the food groups respondents reported adequate intake of grains and cereals (2.3%), vegetables (21.8%), fruits (29.3%) and dairy or alternatives (52.6%). Adequate intake of lean meats and alternatives was achieved by 78.2% of respondents, and approximately the same proportion (82%) consumed within the recommended range for discretionary

items. Altogether this data suggests that Australians with fibromyalgia may be consuming insufficient total energy, and a low intake of plant-derived foods and dairy and alternatives may put them at risk of inadequate intake of vitamins, minerals, and other beneficial compounds for example, dietary polyphenols (Luca et al., 2020). Given the demographic of the sampled cohort, which was predominantly women in middle age or older, their eating pattern could indicate an increased risk of some conditions associated with nutrient deficiency, such as, osteoporosis and iron deficiency. Iron may be especially important for people with fibromyalgia given that symptoms of iron deficiency and anaemia include fatigue which could exacerbate fatigue associated with their condition itself (Vincent et al., 2013). In a study of 100 Turkish fibromyalgia patients, the frequency of iron deficiency was higher than a control group without fibromyalgia, although dietary intake of iron rich foods and supplements was not assessed by the authors (Okan et al., 2019). Therefore, future work should look at the risk of nutrient deficiencies in Australians with fibromyalgia.

Respondents of the current study reported the frequency of dietary fats consumed over the previous 14 days, olive oil (79%), animal butter (61%), and coconut oil (36%). High intake of monounsaturated fats, including olive oil, are included in an anti-inflammatory diet and is reported to be beneficial for fibromyalgia pain (Correa-Rodriguez et al., 2019). For instance, Rus et al. (2020) found improvements in effects sizes for cardiovascular blood serum biomarkers of 30 fibromyalgia participants when 50 mL of extra virgin olive oil or refined olive oil was supplemented for three weeks. Cortisol levels improved (extra virgin olive oil ES: 0.636, refined olive oil ES: 1.205) and platelet distribution width improved (extra virgin ES: 0.073, refined olive oil ES: 0.967) (Rus et al., 2020). However, the sample from the current study also reported frequent intake of animal butter, which is high in saturated fat. A diet high in saturated fats increases total plasma low-density lipids cholesterol and is associated with increased cardiovascular risk markers for obesity and hypertension (Julibert et al., 2019). Although the quantity of dietary fats consumed by the current cohort is unknown and intake of high volumes may impact pain symptoms. Pain management is reported as in Chapter Two of the thesis, and it was highlighted that this group are using many prescribed pharmacotherapies to treat their fibromyalgia pain symptoms and reported a lack of effectiveness for these pharmacotherapies. therefore, more research is needed to determine whether intake of certain dietary fats aid in pain symptoms for this cohort.

In the hope of managing their fibromyalgia symptoms, 76% of respondents reported to trial at least one different diet. Of the total number of participants who reported using diets (helpful or not helpful) for fibromyalgia symptoms, the most frequent diets trialled were exclusion type diets: the low sugar diet (81%), alcohol-free diet (75%) and the gluten-free diet (64%). The reported effectiveness of all diets trialled was varied. However, 41% reported the gluten-free diet to help manage their fibromyalgia symptoms, and it has been reported in the literature to benefit fibromyalgia symptoms. Pagliai et al. (2020) included for review four studies utilising a gluten-free diet (total of 159

participants) and concluded that the gluten-free diet was beneficial for symptoms of pain, fatigue, weight management, and impact questionnaire scores for fibromyalgia participants. However, there were limited quality study designs in the review, and higher-quality studies are needed to comprehensively determine the effectiveness of gluten-free and other diets for fibromyalgia symptoms. For instance, only one of the studies investigating a gluten-free diet had a comparative group (40 participants who underwent a hypocaloric diet versus 35 participants in the gluten-free diet group) (Slim et al., 2015). Thus, further studies are required into the effectiveness of gluten-free diets in the management of fibromyalgia, as the evidence is limited, and even in this cohort, the results varied with 24% of respondents indicating that this dietary pattern did not help to manage their symptoms. Notably, most respondents of the current study had tried a low sugar diet and a gluten-free diet, both of which would be associated with a lower intake of dietary carbohydrates when almost all respondents also failed to meet the recommended intake of grains and cereals. This suggests that Australians with fibromyalgia may have a low intake of dietary carbohydrates which may impact on their ability to undertake greater levels of moderate to vigorous exercise intensity.

There is a lack of high-quality research for dietary interventions and exercise modalities for fibromyalgia symptoms and associated comorbidities, therefore, it is difficult to determine whether certain dietary changes reported by respondents impact reports of pain symptoms and pain severity. Although it is reasonable to assume that if the cohort increased their adherence to moderate intensity exercise and ate according to recommending guidelines, the overall burden of the disease would be reduced. Limitations facing this study included a lack of questioning regarding whether exercise routines were prescribed by an exercise professional, or whether it was self-prescribed. There were also limitations regarding dietary fat intake questions and whether respondents sought clinical advice from an accredited practising dietitian for their dietary changes. To understand the benefit of moderate resistance exercise for fibromyalgia symptoms and, determine whether certain dietary interventions, for example restricted intake of saturated fats, reduces the severity of fibrmoyalgia symptoms more research is needed to support those who currently find no relief with prescribed pharmacotherapies.

Conclusion

Fibromyalgia is a condition that impacts the patients' quality of life, with symptoms of intense pain and digestive issues. This sample of Australian fibromyalgia patients use a variety of lifestyle interventions to manage their symptoms. These interventions included regular walking exercise and various dietary changes. Respondents reported low durations of physical activity and, low numbers reported resistance exercise. A low number of respondents also reported to eat according to Australian guidelines for healthy eating. A large portion of respondents reported to trial a variety of diets for symptom management, with varying degrees of effectiveness. Considering the complexity of this syndrome, prevalence of dietary alterations, and lack of resistance exercise it is perceived that this cohort have a reliance on pain medications to manage their pain. The current study is an initial

investigation into the lifestyles of a sample of the Australian fibromyalgia population. Lifestyle interventions for fibromyalgia in Australia is under-researched and it is unclear what modalities and durations of physical activity, and what dietary interventions are beneficial for the symptoms and comorbidities of fibromyalgia.

4. Chapter Four: Thesis Summary and Conclusions

Fibromyalgia is a complex, multifactorial condition with incompletely known aetiology, affecting 2-5% of the population (Tzadok & Ablin, 2020). Signs and symptoms of fibromyalgia can be debilitating as pain is experienced frequently and accompanied by many comorbidities. Despite its prevalence, very little is known about Australians with fibromyalgia and their management options. This research aimed to investigate Australians with fibromyalgia, including how they manage their symptoms and what the cohort's lifestyle habits are. This study also aimed to understand whether the cohort find relief from their pain symptoms and if they are satisfied using pharmacotherapies. We identified that this cohort of Australians with a fibromyalgia diagnosis presented with fibromyalgia symptoms that are commonly reported in the published literature, which includes widespread musculoskeletal pain, anxiety and depression, and suicidal ideation. A large proportion of this cohort also experience irritable bowel syndrome which is commonly reported as a fibromyalgia comorbidity. Novel findings of the study were the cohorts' reported medically prescribed therapies, which were higher in average medication per patient compared to similar fibromyalgia population studies. This study also found that all respondents reported to use self-prescribed pain therapies, which had varied reports for effectiveness. This study also found that respondents reported low physical activity levels and reported using various dietary alterations for fibromyalgia symptoms.

There are several limitations to the current study. Mostly all the respondents self-reported their sex to be female, a portion (n = 6) reported being male. In 2016, the criteria for fibromyalgia decreased the female: male ratio to ~1.5:1 (Tzadok & Ablin, 2020; Wolfe et al., 2018). There may be a bias from diagnosing general practitioners or a lack of males being referred and diagnosed by Rheumatologists. However, the lack of males using online social fibromyalgia groups may under-represent males in this study.

Detailed data on this cohort’s demographical data is missing from this study: body weight, height, ethnicity, occupation, living situation, or relationship status can help identify subgroups of Australians with fibromyalgia. Additionally, the current study did not capture medical and medication history, including medically and self-prescribed pharmacotherapy dosages, medically prescribed physical activity, or whether respondents use allied health practitioners for managing their symptoms. A significant limitation of the current study was the lack of quantitative measures of actual exercise volumes and uniform numerical scale ratings for reports of pain, pain after taking medications, satisfaction scores of medication use or for diets trialled.

Future work should investigate the listed limitations above to further develop our understanding of fibromyalgia and its effective treatments. Some pharmacotherapies prescribed for fibromyalgia symptoms are based on the inference that these therapies will have analgesic effects because there is a therapeutic effect for cohorts with neuropathic pain (Cooper et al., 2017). The use of medicinal

cannabis was prevalent amongst this cohort, and therefore future work should focus on the combination of medicinal cannabis with more commonly prescribed pain medications, paracetamol, amitriptyline, and duloxetine.

There is an opportunity to research common exercise modalities for nociplastic pain in fibromyalgia cohorts. Traditional exercise modes have employed working up to near-maximal loads or high intensities, which is detrimental for muscular fatigue/failure and exacerbating nociplastic pain in this cohort. Exercise trials on fibromyalgia participants, using methods of moderate volumes and intensities, for example velocity loss training allow for safe monitoring phases of health peaks, while capturing increases in strength outcomes along with disease impact scores, and quality of life measures may be beneficial for this cohort.

To date, there have been limited studies investigating effective interventions for currently prescribed pharmacotherapies, exercise therapies and dietary interventions for fibromyalgia disease management. The impact of fibromyalgia on the Australian community is presently under-researched, and there are several opportunities for research to validate what is known and inferred regarding fibromyalgia symptoms and, reliable and valid interventions. Research studies investigating innovations in pharmacotherapies, lifestyle interventions and pain management strategies will further develop guidelines for fibromyalgia treatment and help those currently finding no relief from current management strategies.

5. References

Abdel Shaheed, C., Ferreira, G., Dmitritchenko, A., McLachlan, A., Day, R. O., Saragiotto, B., Lin, C., Langendyk, V., Stanaway, F., Latimer, J., Kamper, S., McLachlan, H., Ahedi, H., & Maher, C. G. (2021). The efficacy and safety of paracetamol for pain relief: an overview of systematic reviews. *Medical Journal of Australia, n/a*(n/a). https://doi.org/https://doi.org/10.5694/mja2.50992

Ablin, J. N., Oren, A., Cohen, S., Aloush, V., Buskila, D., Elkayam, O., Wollman, Y., & Berman, M. (2012). Prevalence of fibromyalgia in the Israeli population: a population-based study to estimate the prevalence of fibromyalgia in the Israeli population using the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ). *Clin Exp Rheumatol, 30*(6 Suppl 74), 39-43.

Afrisham, R., Paknejad, M., Soliemanifar, O., Sadegh-Nejadi, S., Meshkani, R., & Ashtary-Larky, D. (2019, Apr). The Influence of Psychological Stress on the Initiation and Progression of Diabetes and Cancer. *Int J Endocrinol Metab, 17*(2), e67400. https://doi.org/10.5812/ijem.67400

Agostoni, P., Corrà, U., & Emdin, M. (2017, Jul). Periodic Breathing during Incremental Exercise. *Ann Am Thorac Soc, 14*(Supplement_1), S116-s122. https://doi.org/10.1513/AnnalsATS.201701-003FR

Albrecht, D. S., Forsberg, A., Sandstrom, A., Bergan, C., Kadetoff, D., Protsenko, E., Lampa, J., Lee, Y. C., Hoglund, C. O., Catana, C., Cervenka, S., Akeju, O., Lekander, M., Cohen, G., Halldin, C., Taylor, N., Kim, M., Hooker, J. M., Edwards, R. R., Napadow, V., Kosek, E., & Loggia, M. L. (2019, Jan). Brain glial activation in fibromyalgia - A multi-site positron emission tomography investigation. *Brain Behav Immun, 75*, 72-83. https://doi.org/10.1016/j.bbi.2018.09.018

Almulla, A. F., Al-Hakeim, H. K., Abed, M. S., Carvalho, A. F., & Maes, M. (2020, May 26). Chronic fatigue and fibromyalgia symptoms are key components of deficit schizophrenia and are strongly associated with activated immune-inflammatory pathways. *Schizophr Res*. https://doi.org/10.1016/j.schres.2020.05.003

Aloush, V. (2019, Sep). [FIBROMYALGIA, OBESITY AND ALL THAT LIES IN BETWEEN]. *Harefuah, 158*(9), 587-588.

Alvarez-Gallardo, I. C., Estevez-Lopez, F., Torres-Aguilar, X. C., Segura-Jimenez, V., Borges-Cosic, M., Soriano-Maldonado, A., Camiletti-Moiron, D., Garcia-Rodriguez, I. C., Munguia-Izquierdo, D., Sierras-Robles, A., Delgado-Fernandez, M., & Girela-Rejon, M. J. (2019, Aug 29). Physical activity, sedentary behaviour, physical fitness, and cognitive performance in women with fibromyalgia who engage in reproductive and productive work: the al-Andalus project. *Clin Rheumatol*. https://doi.org/10.1007/s10067-019-04750-8

Alvheim, A. R., Malde, M. K., Osei-Hyiaman, D., Lin, Y. H., Pawlosky, R. J., Madsen, L., Kristiansen, K., Frøyland, L., & Hibbeln, J. R. (2012, Oct). Dietary linoleic acid elevates endogenous 2-AG and

anandamide and induces obesity. *Obesity (Silver Spring), 20*(10), 1984-1994. https://doi.org/10.1038/oby.2012.38

Andrade, C. (2020, 2020/11/01). The Limitations of Online Surveys. *Indian Journal of Psychological Medicine, 42*(6), 575-576. https://doi.org/10.1177/0253717620957496

Andres-Rodriguez, L., Borras, X., Feliu-Soler, A., Perez-Aranda, A., Rozadilla-Sacanell, A., Arranz, B., Montero-Marin, J., Garcia-Campayo, J., Angarita-Osorio, N., Maes, M., & Luciano, J. V. (2019, Aug 29). Machine Learning to Understand the Immune-Inflammatory Pathways in Fibromyalgia. *International Journal Molecular Science, 20*(17). https://doi.org/10.3390/ijms20174231

Arnett, K., Roach, A., Elzy, M., & Jelsone-Swain, L. (2019, Apr). Childhood emotional invalidation and right hemispheric mu suppression during a pain empathy task: An EEG study. *Soc Neurosci, 14*(2), 236-250. https://doi.org/10.1080/17470919.2018.1441905

Arnold, L. M., Goldenberg, D. L., Stanford, S. B., Lalonde, J. K., Sandhu, H. S., Keck, P. E., Jr., Welge, J. A., Bishop, F., Stanford, K. E., Hess, E. V., & Hudson, J. I. (2007, Apr). Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum, 56*(4), 1336-1344. https://doi.org/10.1002/art.22457

Azevedo, L. F., Costa-Pereira, A., Mendonça, L., Dias, C. C., & Castro-Lopes, J. M. (2012, Aug). Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *J Pain, 13*(8), 773-783. https://doi.org/10.1016/j.jpain.2012.05.012

Bäckryd, E., Tanum, L., Lind, A. L., Larsson, A., & Gordh, T. (2017). Evidence of both systemic inflammation and neuroinflammation in fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. *J Pain Res, 10*, 515-525. https://doi.org/10.2147/jpr.s128508

Barakat, A. (2019, May). Revisiting Tramadol: A Multi-Modal Agent for Pain Management. *CNS Drugs, 33*(5), 481-501. https://doi.org/10.1007/s40263-019-00623-5

Beggiato, S., Tomasini, M. C., & Ferraro, L. (2019). Palmitoylethanolamide (PEA) as a Potential Therapeutic Agent in Alzheimer's Disease. *Front Pharmacol, 10*, 821. https://doi.org/10.3389/fphar.2019.00821

Bennett, R. M., Jones, J., Turk, D. C., Russell, I. J., & Matallana, L. (2007, Mar 9). An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord, 8*, 27. https://doi.org/10.1186/1471-2474-8-27

Bennett, R. M., Kamin, M., Karim, R., & Rosenthal, N. (2003, May). Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med, 114*(7), 537-545. https://doi.org/10.1016/s0002-9343(03)00116-5

Berger, A. A., Keefe, J., Winnick, A., Gilbert, E., Eskander, J. P., Yazdi, C., Kaye, A. D., Viswanath, O., & Urits, I. (2020, Sep). Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. *Best Pract Res Clin Anaesthesiol, 34*(3), 617-631. https://doi.org/10.1016/j.bpa.2020.08.010

Bertrand, P. P., Polglaze, K. E., Chen, H., Sandow, S. L., Walduck, A., Jenkins, T. A., Bertrand, R. L., Lomax, A. E., & Liu, L. (2016). Excitability and Synaptic Transmission in the Enteric Nervous System: Does Diet Play a Role? *Adv Exp Med Biol, 891*, 201-211. https://doi.org/10.1007/978-3-319-27592-5_19

Besiroglu, M. D. H., & Dursun, M. D. M. (2019, Jul). The association between fibromyalgia and female sexual dysfunction: a systematic review and meta-analysis of observational studies. *Int J Impot Res, 31*(4), 288-297. https://doi.org/10.1038/s41443-018-0098-3

Bethesda. (2020). LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Book]. *National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Gabapentin. [Updated 2020 Jul 30].* . https://www.ncbi.nlm.nih.gov/books/NBK548252/

Bisaglia, M., Venezia, V., Piccioli, P., Stanzione, S., Porcile, C., Russo, C., Mancini, F., Milanese, C., & Schettini, G. (2002, Jul). Acetaminophen protects hippocampal neurons and PC12 cultures from amyloid beta-peptides induced oxidative stress and reduces NF-kappaB activation. *Neurochem Int, 41*(1), 43-54. https://doi.org/10.1016/s0197-0186(01)00136-x

Bjørklund, G., Dadar, M., Chirumbolo, S., & Aaseth, J. (2018, Jul). Fibromyalgia and nutrition: Therapeutic possibilities? *Biomed Pharmacother, 103*, 531-538. https://doi.org/10.1016/j.biopha.2018.04.056

Bock, K. W., Schrenk, D., Forster, A., Griese, E. U., Mörike, K., Brockmeier, D., & Eichelbaum, M. (1994, Aug). The influence of environmental and genetic factors on CYP2D6, CYP1A2 and UDP-glucuronosyltransferases in man using sparteine, caffeine, and paracetamol as probes. *Pharmacogenetics, 4*(4), 209-218. https://doi.org/10.1097/00008571-199408000-00005

Boehme, R., van Ettinger-Veenstra, H., Olausson, H., Gerdle, B., & Nagi, S. S. (2020, May 18). Anhedonia to Gentle Touch in Fibromyalgia: Normal Sensory Processing but Abnormal Evaluation. *Brain Science, 10*(5). https://doi.org/10.3390/brainsci10050306

Brun, C., McCabe, C. S., & Mercier, C. (2020, May 10). The Contribution of Motor Commands to the Perturbations Induced by Sensorimotor Conflicts in Fibromyalgia. *Neuroscience, 434*, 55-65. https://doi.org/10.1016/j.neuroscience.2020.03.017

Cândea, D. M., & Szentagotai-Tătar, A. (2018, Aug). Shame-proneness, guilt-proneness and anxiety symptoms: A meta-analysis. *J Anxiety Disord, 58*, 78-106. https://doi.org/10.1016/j.janxdis.2018.07.005

Carrillo-Izquierdo, M. D., Slim, M., Hidalgo-Tallon, J., & Calandre, E. P. (2018, Nov). Pelvic floor dysfunction in women with fibromyalgia and control subjects: Prevalence and impact on

overall symptomatology and psychosocial function. *Neurourol Urodyn, 37*(8), 2702-2709. https://doi.org/10.1002/nau.23723

Carta, M. G., Moro, M. F., Pinna, F. L., Testa, G., Cacace, E., Ruggiero, V., Piras, M., Romano, F., Minerba, L., Machado, S., Freire, R. C., Nardi, A. E., & Sancassiani, F. (2018, Nov). The impact of fibromyalgia syndrome and the role of comorbidity with mood and post-traumatic stress disorder in worsening the quality of life. *Int J Soc Psychiatry, 64*(7), 647-655. https://doi.org/10.1177/0020764018795211

Castellana, M., Conte, E., Cignarelli, A., Perrini, S., Giustina, A., Giovanella, L., Giorgino, F., & Trimboli, P. (2020, Mar). Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis. *Rev Endocr Metab Disord, 21*(1), 5-16. https://doi.org/10.1007/s11154-019-09514-y

Cawthon, C. R., & de La Serre, C. B. (2018, Aug 15). Gut bacteria interaction with vagal afferents. *Brain Res, 1693*(Pt B), 134-139. https://doi.org/10.1016/j.brainres.2018.01.012

Cervilla, O., Miro, E., Martinez, M. P., Sanchez, A. I., Sabio, J. M., & Prados, G. (2019, Oct 10). Sleep quality and clinical and psychological manifestations in women with mild systemic lupus erythematosus activity compared to women with fibromyalgia: a preliminary study. *Mod Rheumatol*, 1-22. https://doi.org/10.1080/14397595.2019.1679973

Charoenwoodhipong, P., Harlow, S. D., Marder, W., Hassett, A. L., McCune, W. J., Gordon, C., Helmick, C. G., Barbour, K. E., Wang, L., Mancuso, P., Somers, E. C., & Zick, S. M. (2020, Jul). Dietary Omega Polyunsaturated Fatty Acid Intake and Patient-Reported Outcomes in Systemic Lupus Erythematosus: The Michigan Lupus Epidemiology and Surveillance Program. *Arthritis Care Res (Hoboken), 72*(7), 874-881. https://doi.org/10.1002/acr.23925

Cheatham, S. W., Kolber, M. J., Mokha, G. M., & Hanney, W. J. (2018, Feb). Concurrent validation of a pressure pain threshold scale for individuals with myofascial pain syndrome and fibromyalgia. *J Man Manip Ther, 26*(1), 25-35. https://doi.org/10.1080/10669817.2017.1349592

Clos-Garcia, M., Andrés-Marin, N., Fernández-Eulate, G., Abecia, L., Lavín, J. L., van Liempd, S., Cabrera, D., Royo, F., Valero, A., Errazquin, N., Vega, M. C. G., Govillard, L., Tackett, M. R., Tejada, G., Gónzalez, E., Anguita, J., Bujanda, L., Orcasitas, A. M. C., Aransay, A. M., Maíz, O., López de Munain, A., & Falcón-Pérez, J. M. (2019, Aug). Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. *EBioMedicine, 46*, 499-511. https://doi.org/10.1016/j.ebiom.2019.07.031

Cohen, K., Weizman, A., & Weinstein, A. (2019, May). Positive and Negative Effects of Cannabis and Cannabinoids on Health. *Clin Pharmacol Ther, 105*(5), 1139-1147. https://doi.org/10.1002/cpt.1381

Coluzzi, F., Fornasari, D., Pergolizzi, J., & Romualdi, P. (2017, Apr). From acute to chronic pain: tapentadol in the progressive stages of this disease entity. *Eur Rev Med Pharmacol Sci, 21*(7), 1672-1683.

Cooper, T. E., Derry, S., Wiffen, P. J., & Moore, R. A. (2017, Jan 3). Gabapentin for fibromyalgia pain in adults. *Cochrane Database Syst Rev, 1*(1), Cd012188. https://doi.org/10.1002/14651858.CD012188.pub2

Coppens, E., Van Wambeke, P., Morlion, B., Weltens, N., Giao Ly, H., Tack, J., Luyten, P., & Van Oudenhove, L. (2017, Oct). Prevalence and impact of childhood adversities and post-traumatic stress disorder in women with fibromyalgia and chronic widespread pain. *Eur J Pain, 21*(9), 1582-1590. https://doi.org/10.1002/ejp.1059

Córdova-Palomera, A., Tornador, C., Falcón, C., Bargalló, N., Nenadic, I., Deco, G., & Fañanás, L. (2015). Altered Amygdalar Resting-State Connectivity in Depression is Explained by Both Genes and Environment. *Human brain mapping, 36*. https://doi.org/10.1002/hbm.22876

Corey-Bloom, J., Wolfson, T., Gamst, A., Jin, S., Marcotte, T. D., Bentley, H., & Gouaux, B. (2012). Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 184*(10), 1143-1150. https://doi.org/10.1503/cmaj.110837

Correa-Rodriguez, M., Casas-Barragan, A., Gonzalez-Jimenez, E., Schmidt-RioValle, J., Molina, F., & Aguilar-Ferrandiz, M. E. (2019, Sep 25). Dietary Inflammatory Index Scores Are Associated with Pressure Pain Hypersensitivity in Women with Fibromyalgia. *Pain Med*. https://doi.org/10.1093/pm/pnz238

Costa, Y. M., Conti, P. C., de Faria, F. A., & Bonjardim, L. R. (2017, Mar). Temporomandibular disorders and painful comorbidities: clinical association and underlying mechanisms. *Oral Surg Oral Med Oral Pathol Oral Radiol, 123*(3), 288-297. https://doi.org/10.1016/j.oooo.2016.12.005

Couch, D. G., Tasker, C., Theophilidou, E., Lund, J. N., & O'Sullivan, S. E. (2017, Nov 1). Cannabidiol and palmitoylethanolamide are anti-inflammatory in the acutely inflamed human colon. *Clin Sci (Lond), 131*(21), 2611-2626. https://doi.org/10.1042/cs20171288

Crocq, M. A. (2017, Jun). The history of generalized anxiety disorder as a diagnostic category. *Dialogues Clin Neurosci, 19*(2), 107-116.

D'Onghia, M., Ciaffi, J., Lisi, L., Mancarella, L., Ricci, S., Stefanelli, N., Meliconi, R., & Ursini, F. (2021, Apr). Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. *Semin Arthritis Rheum, 51*(2), 409-424. https://doi.org/10.1016/j.semarthrit.2021.02.007

Dailey, D. L., Frey Law, L. A., Vance, C. G., Rakel, B. A., Merriwether, E. N., Darghosian, L., Golchha, M., Geasland, K. M., Spitz, R., Crofford, L. J., & Sluka, K. A. (2016, Mar 16). Perceived function

and physical performance are associated with pain and fatigue in women with fibromyalgia. *Arthritis Res Ther, 18*, 68. https://doi.org/10.1186/s13075-016-0954-9

Daou, H. N. (2020, Feb 1). Exercise as an anti-inflammatory therapy for cancer cachexia: a focus on interleukin-6 regulation. *Am J Physiol Regul Integr Comp Physiol, 318*(2), R296-r310. https://doi.org/10.1152/ajpregu.00147.2019

Del Giorno, R., Skaper, S., Paladini, A., Varrassi, G., & Coaccioli, S. (2015, Dec). Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies. *Pain Ther, 4*(2), 169-178. https://doi.org/10.1007/s40122-015-0038-6

Delgado, P. L., & Moreno, F. A. (2000). Role of norepinephrine in depression. *J Clin Psychiatry, 61 Suppl 1*, 5-12.

Department of Health, A. G. (2020). *The Australian Dietary Guidelines* https://www.eatforhealth.gov.au/guidelines

Department of Health, A. G. (2021, September 2021). *Australian Government Department of Health Physical activity and exercise guidelines for all Australians*. https://www.health.gov.au/health-topics/physical-activity-and-exercise/physical-activity-and-exercise-guidelines-for-all-australians

Derijks, L. J. J., Wong, D. R., Hommes, D. W., & van Bodegraven, A. A. (2018, Sep). Clinical Pharmacokinetic and Pharmacodynamic Considerations in the Treatment of Inflammatory Bowel Disease. *Clin Pharmacokinet, 57*(9), 1075-1106. https://doi.org/10.1007/s40262-018-0639-4

Derry, S., Cording, M., Wiffen, P. J., Law, S., Phillips, T., & Moore, R. A. (2016, Sep 29). Pregabalin for pain in fibromyalgia in adults. *Cochrane Database Syst Rev, 9*(9), Cd011790. https://doi.org/10.1002/14651858.CD011790.pub2

Derry, S., Wiffen, P. J., Häuser, W., Mücke, M., Tölle, T. R., Bell, R. F., & Moore, R. A. (2017, Mar 27). Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. *Cochrane Database Syst Rev, 3*(3), Cd012332. https://doi.org/10.1002/14651858.CD012332.pub2

Dionne, J., Ford, A. C., Yuan, Y., Chey, W. D., Lacy, B. E., Saito, Y. A., Quigley, E. M. M., & Moayyedi, P. (2018, Sep). A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPs Diet in Treating Symptoms of Irritable Bowel Syndrome. *Am J Gastroenterol, 113*(9), 1290-1300. https://doi.org/10.1038/s41395-018-0195-4

Erdrich, S., Hawrelak, J. A., Myers, S. P., & Harnett, J. E. (2020, Mar 20). Determining the association between fibromyalgia, the gut microbiome and its biomarkers: A systematic review. *BMC Musculoskelet Disord, 21*(1), 181. https://doi.org/10.1186/s12891-020-03201-9

Ericsson, A., Palstam, A., Larsson, A., Lofgren, M., Bileviciute-Ljungar, I., Bjersing, J., Gerdle, B., Kosek, E., & Mannerkorpi, K. (2016, Jul 30). Resistance exercise improves physical fatigue in women with fibromyalgia: a randomized controlled trial. *Arthritis Res Ther, 18*, 176. https://doi.org/10.1186/s13075-016-1073-3

Fitzcharles, M. A., Shir, Y., Ablin, J. N., Buskila, D., Amital, H., Henningsen, P., & Häuser, W. (2013). Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. *Evid Based Complement Alternat Med, 2013*, 528952. https://doi.org/10.1155/2013/528952

Frieboes, R. M., Antonijevic, I. A., Held, K., Murck, H., Pollmächer, T., Uhr, M., & Steiger, A. (2004, Aug). Hexarelin decreases slow-wave sleep and stimulates the secretion of GH, ACTH, cortisol and prolactin during sleep in healthy volunteers. *Psychoneuroendocrinology, 29*(7), 851-860. https://doi.org/10.1016/s0306-4530(03)00152-5

Galvez-Sanchez, C. M., Montoro, C. I., Duschek, S., & Del Paso, G. A. R. (2020, Feb 29). Pain catastrophizing mediates the negative influence of pain and trait-anxiety on health-related quality of life in fibromyalgia. *Qual Life Res*. https://doi.org/10.1007/s11136-020-02457-x

García-Rayado, G., Navarro, M., & Lanas, A. (2018, Oct). NSAID induced gastrointestinal damage and designing GI-sparing NSAIDs. *Expert Rev Clin Pharmacol, 11*(10), 1031-1043. https://doi.org/10.1080/17512433.2018.1516143

Gaskell, H., Moore, R. A., Derry, S., & Stannard, C. (2016, Sep 1). Oxycodone for pain in fibromyalgia in adults. *Cochrane Database Syst Rev, 9*(9), Cd012329. https://doi.org/10.1002/14651858.Cd012329

Giorgi, V., Bongiovanni, S., Atzeni, F., Marotto, D., Salaffi, F., & Sarzi-Puttini, P. (2020, Jan-Feb). Adding medical cannabis to standard analgesic treatment for fibromyalgia: a prospective observational study. *Clin Exp Rheumatol, 38 Suppl 123*(1), 53-59.

Gonzalez-Vives, S., Diaz-Marsa, M., De la Vega, I., Palomares, N., Vazquez, S., Lopez-Villatoro, J. M., Palomo, T., & Carrasco, J. L. (2019, Oct 8). Hypothalamic-Pituitary axis response to a 0.25-mg dexamethasone test in women with fibromyalgia. *Stress*, 1-28. https://doi.org/10.1080/10253890.2019.1678024

Gonzalez, J. L., Alonso-Fernandez, M., Matias-Pompa, B., Carretero, I., Nieto-Bona, M. P., & Lopez-Lopez, A. (2019, May 1). Cardiovascular Responses of Women with Fibromyalgia to a Laboratory Stressor: Does Post-traumatic Stress Disorder Comorbidity Matter? *Pain Med, 20*(5), 988-999. https://doi.org/10.1093/pm/pny210

Guida, F., Luongo, L., Boccella, S., Giordano, M. E., Romano, R., Bellini, G., Manzo, I., Furiano, A., Rizzo, A., Imperatore, R., Iannotti, F. A., D'Aniello, E., Piscitelli, F., Sca Rossi, F., Cristino, L., Di Marzo, V., de Novellis, V., & Maione, S. (2017, Mar 23). Palmitoylethanolamide induces microglia changes associated with increased migration and phagocytic activity: involvement of the CB2 receptor. *Sci Rep, 7*(1), 375. https://doi.org/10.1038/s41598-017-00342-1

Guo, J., & Ikeda, S. R. (2004, Mar). Endocannabinoids modulate N-type calcium channels and G-protein-coupled inwardly rectifying potassium channels via CB1 cannabinoid receptors heterologously expressed in mammalian neurons. *Mol Pharmacol, 65*(3), 665-674. https://doi.org/10.1124/mol.65.3.665

Guymer, E. (2020, Aug 2020). *Musculoskeletal Australia; Fibromyalgia* https://www.msk.org.au/fibromyalgia/

Hall, K. D., & Kahan, S. (2018). Maintenance of Lost Weight and Long-Term Management of Obesity. *The Medical clinics of North America, 102*(1), 183-197. https://doi.org/10.1016/j.mcna.2017.08.012

Hamaguchi, T., Tayama, J., Suzuki, M., Nakaya, N., Takizawa, H., Koizumi, K., Amano, Y., Kanazawa, M., & Fukudo, S. (2020). The effects of locomotor activity on gastrointestinal symptoms of irritable bowel syndrome among younger people: An observational study. *PLoS One, 15*(5), e0234089. https://doi.org/10.1371/journal.pone.0234089

Hamed, S. A. (2018, Jul/Aug). Sexual Dysfunctions Induced by Pregabalin. *Clin Neuropharmacol, 41*(4), 116-122. https://doi.org/10.1097/wnf.0000000000000286

Hauser, W., Hoffmann, E. M., Wolfe, F., Worthing, A. B., Stahl, N., Rothenberg, R., & Walitt, B. (2015, Jan-Feb). Self-reported childhood maltreatment, lifelong traumatic events and mental disorders in fibromyalgia syndrome: a comparison of US and German outpatients. *Clin Exp Rheumatol, 33*(1 Suppl 88), S86-92. https://www.ncbi.nlm.nih.gov/pubmed/25786049

Hawley, J. A., & Leckey, J. J. (2015, Nov). Carbohydrate Dependence During Prolonged, Intense Endurance Exercise. *Sports Med, 45 Suppl 1*(Suppl 1), S5-12. https://doi.org/10.1007/s40279-015-0400-1

Hazra, S., Venkataraman, S., Handa, G., Yadav, S. L., Wadhwa, S., Singh, U., Kochhar, K. P., Deepak, K. K., & Sarkar, K. (2020). A Cross-Sectional Study on Central Sensitization and Autonomic Changes in Fibromyalgia. *Front Neurosci, 14*, 788. https://doi.org/10.3389/fnins.2020.00788

Heredia-Jimenez, J., Orantes-Gonzalez, E., & Soto-Hermoso, V. M. (2016, Mar). Variability of gait, bilateral coordination, and asymmetry in women with fibromyalgia. *Gait Posture, 45*, 41-44. https://doi.org/10.1016/j.gaitpost.2016.01.008

Hernandez-Leon, A., De la Luz-Cuellar, Y. E., Granados-Soto, V., Gonzalez-Trujano, M. E., & Fernandez-Guasti, A. (2018, Jan). Sex differences and estradiol involvement in hyperalgesia and allodynia in an experimental model of fibromyalgia. *Horm Behav, 97*, 39-46. https://doi.org/10.1016/j.yhbeh.2017.10.011

Hsu, E. S. (2011, Nov). Acute and chronic pain management in fibromyalgia: updates on pharmacotherapy. *Am J Ther, 18*(6), 487-509. https://doi.org/10.1097/MJT.0b013e3181d6b6d4

Izquierdo-Alventosa, R., Inglés, M., Cortés-Amador, S., Gimeno-Mallench, L., Chirivella-Garrido, J., Kropotov, J., & Serra-Añó, P. (2020, May 21). Low-Intensity Physical Exercise Improves Pain Catastrophizing and Other Psychological and Physical Aspects in Women with Fibromyalgia: A Randomized Controlled Trial. *Int J Environ Res Public Health, 17*(10). https://doi.org/10.3390/ijerph17103634

Johal, H., Devji, T., Chang, Y., Simone, J., Vannabouathong, C., & Bhandari, M. (2020). Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. *Clin Med Insights Arthritis Musculoskelet Disord, 13*, 1179544120906461. https://doi.org/10.1177/1179544120906461

Julibert, A., Bibiloni, M. D. M., & Tur, J. A. (2019, Sep). Dietary fat intake and metabolic syndrome in adults: A systematic review. *Nutr Metab Cardiovasc Dis, 29*(9), 887-905. https://doi.org/10.1016/j.numecd.2019.05.055

Kapuczinski, A., Soyfoo, M. S., De Breucker, S., & Margaux, J. (2021, Aug 21). Assessment of sarcopenia in patients with fibromyalgia. *Rheumatol Int*. https://doi.org/10.1007/s00296-021-04973-6

Karaş, H., Çetingök, H., İlişer, R., Çarpar, E., & Kaşer, M. (2020, May 13). Childhood and adult attention deficit hyperactivity disorder symptoms in fibromyalgia: associations with depression, anxiety and disease impact. *Int J Psychiatry Clin Pract*, 1-7. https://doi.org/10.1080/13651501.2020.1764585

Katz, D., Katz, I., Porat-Katz, B. S., & Shoenfeld, Y. (2017, Feb). Medical cannabis: Another piece in the mosaic of autoimmunity? *Clin Pharmacol Ther, 101*(2), 230-238. https://doi.org/10.1002/cpt.568

Katz, R. S., Wolfe, F., & Michaud, K. (2006, Jan). Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis Rheum, 54*(1), 169-176. https://doi.org/10.1002/art.21533

Kawka, M., Erridge, S., Holvey, C., Coomber, R., Usmani, A., Sajad, M., Platt, M. W., Rucker, J. J., & Sodergren, M. H. (2021, Sep 2). Clinical outcome data of first cohort of chronic pain patients treated with cannabis-based sublingual oils in the United Kingdom - analysis from the UK Medical Cannabis Registry. *J Clin Pharmacol*. https://doi.org/10.1002/jcph.1961

Kia, S., & Choy, E. (2017, May 8). Update on Treatment Guideline in Fibromyalgia Syndrome with Focus on Pharmacology. *Biomedicines, 5*(2). https://doi.org/10.3390/biomedicines5020020

Kim, Y. S., Kim, K. M., Lee, D. J., Kim, B. T., Park, S. B., Cho, D. Y., Suh, C. H., Kim, H. A., Park, R. W., & Joo, N. S. (2011, Oct). Women with fibromyalgia have lower levels of calcium, magnesium, iron and manganese in hair mineral analysis. *J Korean Med Sci, 26*(10), 1253-1257. https://doi.org/10.3346/jkms.2011.26.10.1253

Kistler-Fischbacher, M., Weeks, B. K., & Beck, B. R. (2021, Feb). The effect of exercise intensity on bone in postmenopausal women (part 2): A meta-analysis. *Bone, 143*, 115697. https://doi.org/10.1016/j.bone.2020.115697

Krumina, A., Chapenko, S., Kenina, V., Mihailova, M., Logina, I., Rasa, S., Gintere, S., Viksna, L., Svirskis, S., & Murovska, M. (2019, Apr). The role of HHV-6 and HHV-7 infections in the development of fibromyalgia. *J Neurovirol, 25*(2), 194-207. https://doi.org/10.1007/s13365-018-0703-8

Larson, A. A., Pardo, J. V., & Pasley, J. D. (2014, Jun). Review of overlap between thermoregulation and pain modulation in fibromyalgia. *Clin J Pain, 30*(6), 544-555. https://doi.org/10.1097/AJP.0b013e3182a0e383

Larsson, A., Palstam, A., Lofgren, M., Ernberg, M., Bjersing, J., Bileviciute-Ljungar, I., Gerdle, B., Kosek, E., & Mannerkorpi, K. (2015, Jun 18). Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia--a randomized controlled trial. *Arthritis Res Ther, 17*, 161. https://doi.org/10.1186/s13075-015-0679-1

Levine, D., & Horesh, D. (2020). Suicidality in Fibromyalgia: A Systematic Review of the Literature. *Front Psychiatry, 11*, 535368. https://doi.org/10.3389/fpsyt.2020.535368

Lintzeris, N., Mills, L., Suraev, A., Bravo, M., Arkell, T., Arnold, J. C., Benson, M. J., & McGregor, I. S. (2020, 2020/06/08). Medical cannabis use in the Australian community following introduction of legal access: the 2018–2019 Online Cross-Sectional Cannabis as Medicine Survey (CAMS-18). *Harm Reduction Journal, 17*(1), 37. https://doi.org/10.1186/s12954-020-00377-0

Lobo, M. M. M. T., Paiva, E. d. S., Andretta, A., & Schieferdecker, M. E. M. (2014, 2014/07/01/). Body composition by dual-energy x-ray absorptiometry in women with fibromyalgia. *Revista Brasileira de Reumatologia, 54*(4), 273-278. https://doi.org/https://doi.org/10.1016/j.rbr.2014.03.024

Lowry, E., Marley, J., McVeigh, J. G., McSorley, E., Allsopp, P., & Kerr, D. (2020, Aug 31). Dietary Interventions in the Management of Fibromyalgia: A Systematic Review and Best-Evidence Synthesis. *Nutrients, 12*(9). https://doi.org/10.3390/nu12092664

Luca, S. V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotosoaie, A. C., & Trifan, A. (2020). Bioactivity of dietary polyphenols: The role of metabolites. *Crit Rev Food Sci Nutr, 60*(4), 626-659. https://doi.org/10.1080/10408398.2018.1546669

Mazzuoli-Weber, G., & Schemann, M. (2015). Mechanosensitivity in the enteric nervous system. *Front Cell Neurosci, 9*, 408. https://doi.org/10.3389/fncel.2015.00408

MIMS. (2020). Monthly Index of Medical Specialties. https://www.mimsonline.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searc

hKeyword=palexia&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=96470001_2

Moayedi, M., & Davis, K. D. (2013, Jan). Theories of pain: from specificity to gate control. *J Neurophysiol, 109*(1), 5-12. https://doi.org/10.1152/jn.00457.2012

Moore, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2015, Jul 6). Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev, 2015*(7), Cd008242. https://doi.org/10.1002/14651858.CD008242.pub3

Mücke, M., Phillips, T., Radbruch, L., Petzke, F., & Häuser, W. (2018, Mar 7). Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev, 3*(3), Cd012182. https://doi.org/10.1002/14651858.CD012182.pub2

Mukerji, B., Mukerji, V., Alpert, M. A., & Selukar, R. (1995, May). The prevalence of rheumatologic disorders in patients with chest pain and angiographically normal coronary arteries. *Angiology, 46*(5), 425-430. https://doi.org/10.1177/000331979504600510

Neumann, L., & Buskila, D. (2003, Oct). Epidemiology of fibromyalgia. *Curr Pain Headache Rep, 7*(5), 362-368. https://doi.org/10.1007/s11916-003-0035-z

Norton, K., Norton, L., & Sadgrove, D. (2010). Position statement on physical activity and exercise intensity terminology. *Journal of science and medicine in sport, 13*(5), 496-502.

Niesters, M., Proto, P. L., Aarts, L., Sarton, E. Y., Drewes, A. M., & Dahan, A. (2014, Jul). Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth, 113*(1), 148-156. https://doi.org/10.1093/bja/aeu056

O'Connor, S. R., Tully, M. A., Ryan, B., Bleakley, C. M., Baxter, G. D., Bradley, J. M., & McDonough, S. M. (2015, Apr). Walking exercise for chronic musculoskeletal pain: systematic review and meta-analysis. *Arch Phys Med Rehabil, 96*(4), 724-734.e723. https://doi.org/10.1016/j.apmr.2014.12.003

Okan, S., Caglıyan Turk, A., Sıvgın, H., Ozsoy, F., & Okan, F. (2019, Dec 31). Association of ferritin levels with depression, anxiety, sleep quality, and physical functioning in patients with fibromyalgia syndrome: a cross-sectional study. *Croat Med J, 60*(6), 515-520. https://doi.org/10.3325/cmj.2019.60.515

Ordóñez-Carrasco, J. L., Sánchez-Castelló, M., Calandre, E. P., Cuadrado-Guirado, I., & Rojas-Tejada, A. J. (2020, Dec 30). Suicidal Ideation Profiles in Patients with Fibromyalgia Using Transdiagnostic Psychological and Fibromyalgia-Associated Variables. *Int J Environ Res Public Health, 18*(1). https://doi.org/10.3390/ijerph18010209

Pagliai, G., Giangrandi, I., Dinu, M., Sofi, F., & Colombini, B. (2020, Aug 20). Nutritional Interventions in the Management of Fibromyalgia Syndrome. *Nutrients, 12*(9). https://doi.org/10.3390/nu12092525

Pagliusi, M., Jr., Bonet, I. J. M., Lemes, J. B. P., Oliveira, A. L. L., Carvalho, N. S., Tambeli, C. H., Parada, C. A., & Sartori, C. R. (2020, May 5). Social defeat stress-induced hyperalgesia is mediated by nav 1.8(+) nociceptive fibers. *Neurosci Lett, 729*, 135006. https://doi.org/10.1016/j.neulet.2020.135006

Petrosino, S., Verde, R., Vaia, M., Allara, M., Iuvone, T., & Di Marzo, V. (2018, Jun). Anti-inflammatory Properties of Cannabidiol, a Nonpsychotropic Cannabinoid, in Experimental Allergic Contact Dermatitis. *J Pharmacol Exp Ther, 365*(3), 652-663. https://doi.org/10.1124/jpet.117.244368

Preuss, C. V., Kalava, A., & King, K. C. (2021). Prescription of Controlled Substances: Benefits and Risks. In *StatPearls*. StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.

Qiu, Y., Zhang, T. J., Meng, L. B., Cheng, X. T., & Hua, Z. (2020, Feb 14). Bioinformatics analysis of gene and microRNA targets for fibromyalgia. *Clin Exp Rheumatol*.

Ravikoff Allegretti, J., Courtwright, A., Lucci, M., Korzenik, J. R., & Levine, J. (2013, Dec). Marijuana use patterns among patients with inflammatory bowel disease. *Inflamm Bowel Dis, 19*(13), 2809-2814. https://doi.org/10.1097/01.Mib.0000435851.94391.37

Rico-Villademoros, F., Postigo-Martin, P., Garcia-Leiva, J. M., Ordonez-Carrasco, J. L., & Calandre, E. P. (2020, Jan-Feb). Patterns of pharmacologic and non-pharmacologic treatment, treatment satisfaction and perceived tolerability in patients with fibromyalgia: a patients' survey. *Clin Exp Rheumatol, 38 Suppl 123*(1), 72-78. https://www.ncbi.nlm.nih.gov/pubmed/32116211

Rico-Villademoros, F., Slim, M., & Calandre, E. P. (2015, Oct). Amitriptyline for the treatment of fibromyalgia: a comprehensive review. *Expert Rev Neurother, 15*(10), 1123-1150. https://doi.org/10.1586/14737175.2015.1091726

Riva, R., Mork, P. J., Westgaard, R. H., Okkenhaug Johansen, T., & Lundberg, U. (2012, Jan). Catecholamines and heart rate in female fibromyalgia patients. *J Psychosom Res, 72*(1), 51-57. https://doi.org/10.1016/j.jpsychores.2011.09.010

Román, G. C., Jackson, R. E., Gadhia, R., Román, A. N., & Reis, J. (2019, Dec). Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. *Rev Neurol (Paris), 175*(10), 724-741. https://doi.org/10.1016/j.neurol.2019.08.005

Roman, P., Estévez, A. F., Miras, A., Sánchez-Labraca, N., Cañadas, F., Vivas, A. B., & Cardona, D. (2018). A Pilot Randomized Controlled Trial to Explore Cognitive and Emotional Effects of Probiotics in Fibromyalgia. *Scientific reports, 8*(1), 10965. https://doi.org/10.1038/s41598-018-29388-5

Rus, A., Molina, F., Martínez-Ramírez, M. J., Aguilar-Ferrándiz, M. E., Carmona, R., & Del Moral, M. L. (2020, Mar 27). Effects of Olive Oil Consumption on Cardiovascular Risk Factors in Patients with Fibromyalgia. *Nutrients, 12*(4). https://doi.org/10.3390/nu12040918

Rus, A., Molina, F., Ramos, M. M., Martínez-Ramírez, M. J., & Del Moral, M. L. (2017, Jan). Extra Virgin Olive Oil Improves Oxidative Stress, Functional Capacity, and Health-Related Psychological Status in Patients With Fibromyalgia: A Preliminary Study. *Biol Res Nurs, 19*(1), 106-115. https://doi.org/10.1177/1099800416659370

Russo, E. (2016 (a)). Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis Cannabinoid Res, 1*(1), 154-165. https://doi.org/10.1089/can.2016.0009

Russo, E. (2016 (b)). Beyond Cannabis: Plants and the Endocannabinoid System. *Trends in Pharmacological Sciences, 37*. https://doi.org/10.1016/j.tips.2016.04.005

Sagy, I., Bar-Lev Schleider, L., Ma, S., Abu-Shakra, M., & Novack, V. (2019). Safety and Efficacy of Medical Cannabis in Fibromyalgia.

Sampaio, R. A. C., Sewo Sampaio, P. Y., Uchida, M. C., & Arai, H. (2020). Management of Dynapenia, Sarcopenia, and Frailty: The Role of Physical Exercise. *J Aging Res, 2020*, 8186769. https://doi.org/10.1155/2020/8186769

Saragiotto, B. T., Machado, G. C., Ferreira, M. L., Pinheiro, M. B., Abdel Shaheed, C., & Maher, C. G. (2016, Jun 7). Paracetamol for low back pain. *Cochrane Database Syst Rev, 2016*(6), Cd012230. https://doi.org/10.1002/14651858.Cd012230

Sayın, S., Yurdakul, F. G., Sivas, F., & Bodur, H. (2020, Aug 7). Is fibromyalgia frequency increasing in axial spondyloarthritis? Association with fibromyalgia and biological therapies. *Rheumatol Int*. https://doi.org/10.1007/s00296-020-04670-w

Scarante, F. F., Ribeiro, M. A., Almeida-Santos, A. F., Guimarães, F. S., & Campos, A. C. (2020). Glial Cells and Their Contribution to the Mechanisms of Action of Cannabidiol in Neuropsychiatric Disorders. *Front Pharmacol, 11*, 618065. https://doi.org/10.3389/fphar.2020.618065

Schott, M. (2019, Sep-Oct). Insights on cannabidiol's antiallodynic and anxiolytic mechanisms of action in a model of neuropathic pain. *Pain Rep, 4*(5), e774. https://doi.org/10.1097/pr9.0000000000000774

Schumann, D., Klose, P., Lauche, R., Dobos, G., Langhorst, J., & Cramer, H. (2018, Jan). Low fermentable, oligo-, di-, mono-saccharides and polyol diet in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. *Nutrition, 45*, 24-31. https://doi.org/10.1016/j.nut.2017.07.004

Sempere-Rubio, N., Aguilar-Rodríguez, M., Espí-López, G. V., Cortés-Amador, S., Pascual, E., & Serra-Añó, P. (2018, Nov 15). Impaired Trunk Posture in Women With Fibromyalgia. *Spine (Phila Pa 1976), 43*(22), 1536-1542. https://doi.org/10.1097/brs.0000000000002681

Senna, M. K., Sallam, R. A., Ashour, H. S., & Elarman, M. (2012, Nov). Effect of weight reduction on the quality of life in obese patients with fibromyalgia syndrome: a randomized controlled trial. *Clin Rheumatol, 31*(11), 1591-1597. https://doi.org/10.1007/s10067-012-2053-x

Skaper, S. D., Facci, L., Barbierato, M., Zusso, M., Bruschetta, G., Impellizzeri, D., Cuzzocrea, S., & Giusti, P. (2015, Oct). N-Palmitoylethanolamine and Neuroinflammation: a Novel Therapeutic Strategy of Resolution. *Mol Neurobiol, 52*(2), 1034-1042. https://doi.org/10.1007/s12035-015-9253-8

Slim, M., Molina-Barea, R., Garcia-Leiva, J. M., Rodríguez-Lopez, C. M., Morillas-Arques, P., Rico-Villademoros, F., & Calandre, E. P. (2015, 2015/01/01/). The effects of gluten-free diet versus hypocaloric diet among patients with fibromyalgia experiencing gluten sensitivity symptoms: Protocol for a pilot, open-label, randomized clinical trial. *Contemporary Clinical Trials, 40*, 193-198. https://doi.org/https://doi.org/10.1016/j.cct.2014.11.019

Sosa-Reina, M. D., Nunez-Nagy, S., Gallego-Izquierdo, T., Pecos-Martín, D., Monserrat, J., & Álvarez-Mon, M. (2017). Effectiveness of Therapeutic Exercise in Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Biomed Res Int, 2017*, 2356346. https://doi.org/10.1155/2017/2356346

Stahlberg, L., Palmquist, E., & Nordin, S. (2018, Sep). Intolerance to environmental chemicals and sounds in irritable bowel syndrome: Explained by central sensitization? *J Health Psychol, 23*(10), 1367-1377. https://doi.org/10.1177/1359105316656242

Staud, R., & Smitherman, M. L. (2002, Aug). Peripheral and central sensitization in fibromyalgia: pathogenetic role. *Curr Pain Headache Rep, 6*(4), 259-266. https://doi.org/10.1007/s11916-002-0046-1

Stilling, R. M., van de Wouw, M., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2016, Oct). The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? *Neurochem Int, 99*, 110-132. https://doi.org/10.1016/j.neuint.2016.06.011

Sucher, S., Markova, M., Hornemann, S., Pivovarova, O., Rudovich, N., Thomann, R., Schneeweiss, R., Rohn, S., & Pfeiffer, A. F. H. (2017, Jul). Comparison of the effects of diets high in animal or plant protein on metabolic and cardiovascular markers in type 2 diabetes: A randomized clinical trial. *Diabetes Obes Metab, 19*(7), 944-952. https://doi.org/10.1111/dom.12901

Tai, F. W. D., & McAlindon, M. E. (2018, May). NSAIDs and the small bowel. *Curr Opin Gastroenterol, 34*(3), 175-182. https://doi.org/10.1097/mog.0000000000000427

Taylor, S., Furness, P., Ashe, S., Haywood-Small, S., & Lawson, K. (2020, Jun 26). Comorbid Conditions, Mental Health and Cognitive Functions in Adults with Fibromyalgia. *West J Nurs Res*, 193945920937429. https://doi.org/10.1177/0193945920937429

Theoharides, T. C., Tsilioni, I., & Bawazeer, M. (2019). Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome. *Front Cell Neurosci, 13*, 353. https://doi.org/10.3389/fncel.2019.00353

Thorpe, J., Shum, B., Moore, R. A., Wiffen, P. J., & Gilron, I. (2018, Feb 19). Combination pharmacotherapy for the treatment of fibromyalgia in adults. *Cochrane Database Syst Rev, 2*(2), Cd010585. https://doi.org/10.1002/14651858.CD010585.pub2

Thour, A., & Marwaha, R. (2021). Amitriptyline. In *StatPearls*. StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.

Tomas-Carus, P., Branco, J. C., Raimundo, A., Parraca, J. A., Batalha, N., & Biehl-Printes, C. (2018, Aug). Breathing Exercises Must Be a Real and Effective Intervention to Consider in Women with Fibromyalgia: A Pilot Randomized Controlled Trial. *J Altern Complement Med, 24*(8), 825-832. https://doi.org/10.1089/acm.2017.0335

Trouvin, A. P., & Perrot, S. (2019, Jun). New concepts of pain. *Best Pract Res Clin Rheumatol, 33*(3), 101415. https://doi.org/10.1016/j.berh.2019.04.007

Turcotte, C., Blanchet, M. R., Laviolette, M., & Flamand, N. (2016, Dec). The CB(2) receptor and its role as a regulator of inflammation. *Cell Mol Life Sci, 73*(23), 4449-4470. https://doi.org/10.1007/s00018-016-2300-4

Turner, A. R., Spurling, B. C., & Agrawal, S. (2020). Marijuana Toxicity. In *StatPearls*. StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.

Tzadok, R., & Ablin, J. N. (2020). Current and Emerging Pharmacotherapy for Fibromyalgia [Article]. *Pain Research and Management*, NA. https://link.gale.com/apps/doc/A621001852/AONE?u=anon~596fc184&sid=googleScholar&xid=1e18d9eb

Udit, S., Burton, M., Rutkowski, J. M., Lee, S., Bookout, A. L., Scherer, P. E., Elmquist, J. K., & Gautron, L. (2017). Nav1.8 neurons are involved in limiting acute phase responses to dietary fat. *Molecular Metabolism, 6*(10), 1081-1091. https://doi.org/https://doi.org/10.1016/j.molmet.2017.07.012

Vincent, A., Benzo, R. P., Whipple, M. O., McAllister, S. J., Erwin, P. J., & Saligan, L. N. (2013). Beyond pain in fibromyalgia: insights into the symptom of fatigue. *Arthritis Res Ther, 15*(6), 221. https://doi.org/10.1186/ar4395

Welsch, P., Üçeyler, N., Klose, P., Walitt, B., & Häuser, W. (2018, Feb 28). Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev, 2*(2), Cd010292. https://doi.org/10.1002/14651858.CD010292.pub2

Williams, N. (2017). The Borg Rating of Perceived Exertion (RPE) scale. *Occupational Medicine, 67*(5), 404-405. https://doi.org/10.1093/occmed/kqx063

Wolfe, F., Butler, S. H., Fitzcharles, M., Hauser, W., Katz, R. L., Mease, P. J., Rasker, J. J., Russell, A. S., Russell, I. J., & Walitt, B. (2019, Oct 9). Revised chronic widespread pain criteria: development from and integration with fibromyalgia criteria. *Scand J Pain*. https://doi.org/10.1515/sjpain-2019-0054

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Häuser, W., Katz, R. L., Mease, P. J., Russell, A. S., Russell, I. J., & Walitt, B. (2016, Dec). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum, 46*(3), 319-329. https://doi.org/10.1016/j.semarthrit.2016.08.012

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., Russell, A. S., Russell, I. J., Winfield, J. B., & Yunus, M. B. (2010, May). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken), 62*(5), 600-610. https://doi.org/10.1002/acr.20140

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., Tugwell, P., Campbell, S. M., Abeles, M., Clark, P., & et al. (1990, Feb). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum, 33*(2), 160-172. https://doi.org/10.1002/art.1780330203

Wolfe, F., Walitt, B., Perrot, S., Rasker, J. J., & Häuser, W. (2018). Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PLoS One, 13*(9), e0203755. https://doi.org/10.1371/journal.pone.0203755

Wolfe, F., Walitt, B. T., Katz, R. S., & Häuser, W. (2014). Symptoms, the nature of fibromyalgia, and diagnostic and statistical manual 5 (DSM-5) defined mental illness in patients with rheumatoid arthritis and fibromyalgia. *PLoS One, 9*(2), e88740. https://doi.org/10.1371/journal.pone.0088740

Yunus, M. B. (2012). The prevalence of fibromyalgia in other chronic pain conditions. *Pain Res Treat, 2012*, 584573. https://doi.org/10.1155/2012/584573

Zesiewicz, T. A., & Sullivan, K. L. (2011). Drug-induced hyperkinetic movement disorders by nonneuroleptic agents. *Handb Clin Neurol, 100*, 347-363. https://doi.org/10.1016/b978-0-444-52014-2.00027-6

Zhang, C., Li, S., Pu, F., Fan, Y., & Li, D. (2014). The effect of anatomic variations of circle of Willis on cerebral blood distribution during posture change from supination to standing: a model study. *Biomed Mater Eng, 24*(6), 2371-2380. https://doi.org/10.3233/bme-141050

6. Appendix:

Qualtrics Survey Extract

Victoria University Fibromyalgia Survey

Survey Flow

Block: Introduction/Informed consent (1 Question)
Standard: Demographic (5 Questions)
Standard: Pain symptoms (7 Questions)
Standard: Neurological symptoms (5 Questions)
Standard: Muscle and joint symptoms (5 Questions)
Standard: Symptoms other (3 Questions)
Standard: Alternative therapies (4 Questions)
Standard: Overall satisfaction of treatment regime (2 Questions)
Standard: Dietary Fats (3 Questions)
Standard: General diet (10 Questions)
Standard: Diet Change (7 Questions)
Standard: Exercise (6 Questions)
Standard: End of survey (2 Questions)

Start of Block: Introduction/Informed consent

Q1.1 Thank you for your interest in this Victoria University Fibromyalgia Survey.

This survey is being conducted by researchers from Victoria University researching into the pain management strategies for fibromyalgia. This survey is anonymous, and the discloser of your personal lifestyle choices will not be re-identifiable. The survey will be asking questions regarding your symptoms of fibromyalgia, including medically prescribed (or self-prescribed) medications/therapies, your diet and exercise habits.

For some people, answering questions about the symptoms they suffer with fibromyalgia and how effect their treatments are may cause distress. If you feel that you do need to talk to someone, please contact Beyond Blue on 1300 22 4636 or visit beyondblue.org.au or consult with your health professional. Your participation within this survey is voluntary and you are able to cease the survey at any time.

Questions in this survey may ask whether you use or have ever used illegal substances (depending on your state or territory) for your symptoms of fibromyalgia, however this survey is de-identified and cannot be traced back to you or your personal information in any way.

The survey will take roughly 15 minutes to complete. Data collected in this survey is confidential and will be used for research purposes only. The intent of this research is to contribute to the current knowledge of fibromyalgia and the development and implementation of therapies to assist in pain

management.

Do you give consent to participate in this survey study into fibromyalgia?

- ○ 1. Yes, I give my consent to take the survey (4)
- ○ 2. No, I do not give my consent (5)

Skip To: End of Survey If Thank you for your interest in this Victoria University Fibromyalgia Survey. This survey is bein... = 2. No, I do not give my consent

Page Break

End of Block: Introduction/Informed consent

Start of Block: Demographic

Q2.1 Please select your age?

- 1. 18-24 years (14)
- 2. 25-34 years (15)
- 3. 35-44 years (16)
- 4. 45-54 years (17)
- 5. 55-64 years (18)
- 6. 65-74 years (19)
- 7. 75 years and over (20)

Q2.2 What is your sex?

- 1. Male (1)
- 2. Female (2)
- 3. Other (4) _____
- 4. Prefer not to say (3)

Q2.3 Have you been diagnosed with fibromyalgia?

- 1. Yes (1)
- 2. No (4)

Skip To: End of Survey If Have you been diagnosed with fibromyalgia? = 2. No

Q2.4 At what age were you diagnosed with fibromyalgia? Please indicate in numbers only, for example 35.

_____

Q2.5 What state/territory do you live in?

- ○ 1. Canberra/ACT (14)
- ○ 2. New South Wales (8)
- ○ 3. Northern Territory (13)
- ○ 4. Queensland (11)
- ○ 5. South Australia (12)
- ○ 6. Tasmania (10)
- ○ 7. Victoria (9)
- ○ 8. Western Australia (15)
- ○ 9. If you live outside of Australia please detail the country and state/region. (16)

_____

End of Block: Demographic

Start of Block: Pain symptoms

Q3.1 Please select the symptoms of pain associated with your fibromyalgia (you can select more than one).

- [ ] 1. Headaches/migraines (8)
- [ ] 2. Muscle aches (7)
- [ ] 3. Muscle cramps (10)
- [ ] 4. Widespread pain (9)
- [ ] 5. Add your own (14) _____
- [ ] 6. None (19)

Skip To: End of Block If Please select the symptoms of pain associated with your fibromyalgia (you can select more than one). = 6. None

Q3.2 On average, how frequent are your symptoms of pain?

1- Less than 1 day each month
2- 1-2 days out of the month
3- 3-4 days out of the month
4- 1-2 days out of 7
5- 3-4 days out of 7
6- 5-6 days out of 7
7- Daily, mostly in the evenings
8- Daily, mostly in the morning

	0 1 2 3 4 5 6 7 8
Pain symptoms ()	

Q3.3 Please select the site/s on your body where you feel your reported sensations of pain. Select all appropriate.

- [ ] 1. Head (1)
- [ ] 2. Arms (2)
- [ ] 3. Chest (25)
- [ ] 4. Back (29)
- [ ] 5. Hips (30)
- [ ] 6. Legs (3)
- [ ] 7. Feet (4)
- [ ] 8. Add your own (28) _____

Q3.4 Have you been medically prescribed any of the following to assist with your management of pain symptoms?

- [ ] 1. Paracetamol/Tylenol (1)
- [ ] 2. Amitriptyline/Endep (2)
- [ ] 3. Cannabidiol/CBD oil (3)
- [ ] 4. Duloxetine/Cymbalta (4)
- [ ] 5. Medicinal cannabis (6)
- [ ] 6. Milnacipran/Ixel (7)
- [ ] 7. Oroxine/Levothyroxine (8)
- [ ] 8. Oxycodone/OxyContin (9)
- [ ] 9. PEA/palmitoylethanolamide (14)
- [ ] 10. Physical exercise (5)
- [ ] 11. Pregabalin (10)
- [ ] 12. Tapentadol (11)
- [ ] 13. Tramadol (12)
- [ ] 14. Add your own (13) _____
- [ ] 15. I have not been medically prescribed anything for the management of my pain (15)

Skip To: End of Block If Have you been medically prescribed any of the following to assist with your management of pain sy... = 15. I have not been medically prescribed anything for the management of my pain

Q3.5 On average, how does your pain feel after taking your medication?
1- No pain
2- Unnoticeable pain
3- Low level mild pain
4- Moderate pain, I am aware of it but I can continue my day
5- Distracting pain, I am fully aware of my pain all day
6- Distressing pain, I give up on activities because of my pain
7- Unmanageable, I am aware of my pain and I cannot do most of my activities
8- Intense pain, my pain is so severe I cannot think of anything else, talking and listening are difficult
9- Severe pain, my pain is so severe I can barely talk or move
10- Unable to move, I need someone to assist me

	0	1	2	3	4	5	6	7	8	9	10
Rate your pain after taking your medication? ()											

Carry Forward Selected Choices - Entered Text from "Have you been medically prescribed any of the following to assist with your management of pain symptoms?"

Q3.6 How long have you been using your medication?

1- Less than 1 month
2- 1-3 months
3- 3-5 months
4- 6-12 months
5- 1-2 years
6- 2 years plus

0	1	2	3	4	5	6

1. Paracetamol/Tylenol ()	
2. Amitriptyline/Endep ()	
3. Cannabidiol/CBD oil ()	
4. Duloxetine/Cymbalta ()	
5. Medicinal cannabis ()	
6. Milnacipran/Ixel ()	
7. Oroxine/Levothyroxine ()	
8. Oxycodone/OxyContin ()	
9. PEA/palmitoylethanolamide ()	
10. Physical exercise ()	
11. Pregabalin ()	
12. Tapentadol ()	
13. Tramadol ()	
14. Add your own ()	
15. I have not been medically prescribed anything for the management of my pain ()	

Q3.7 Please select other pain symptoms of fibromyalgia you experience (you can select more than one).

- [ ] 1. Irritable bowel syndrome (1)
- [ ] 2. Pelvic floor dysfunction (2)
- [ ] 3. Temporomandibular dysfunction (3)
- [ ] 4. Add your own (4) _____
- [ ] 5. None (5)

End of Block: Pain symptoms

Start of Block: Neurological symptoms

Q4.1 Please select your symptoms of altered neurological responses associated with fibromyalgia (you can select more than one).

- ☐ 1. Altered hearing (1)
- ☐ 2. Blurred vision (2)
- ☐ 3. Brain fog/memory issues (3)
- ☐ 4. Fatigue (4)
- ☐ 5. Anxiety (5)
- ☐ 6. Depression (6)
- ☐ 7. Problems sleeping (7)
- ☐ 8. Panic attacks (8)
- ☐ 9. Add your own (9) _____
- ☐ 10. None (10)

Skip To: End of Block If Please select your symptoms of altered neurological responses associated with fibromyalgia (you c... = 10. None

Q4.2 How frequent are your symptoms of altered neurological responses?

1- Less than 1 day each month
2- 1-2 days out of the month
3- 3-4 days out of the month
4- 1-2 days out of 7
5- 3-4 days out of 7
6- 5-6 days out of 7
7- Daily, mostly in the evenings
8- Daily, mostly in the morning

0 1 2 3 4 5 6 7 8

How frequent are your symptoms of altered neurological responses? ()	

Q4.3 Have you been medically prescribed any of the following to assist with the management of your neurological symptoms?

- ☐ 1. Amitriptyline/Endep (1)
- ☐ 2. Benzodiazepine (13)
- ☐ 3. Cannabidiol/CBD oil (2)
- ☐ 4. Duloxetine/Cymblta (3)
- ☐ 5. Fluoxetine/Prozac (5)
- ☐ 6. Lexapro (12)
- ☐ 7. Medicinal cannabis (6)
- ☐ 8. Milnacipran/Ixel (7)
- ☐ 9. Palmitoylethanolamide/PEA (8)
- ☐ 10. Physical exercise (4)
- ☐ 11. Pregabalin/Lyrica (9)
- ☐ 12. Valium/Diazapam (10)
- ☐ 13. Zoloft/Sertraline (11)
- ☐ 14. Add your own (14) _____
- ☐ 15. I have not been medically prescribed anything for my neurological symptoms (15)

Skip To: End of Block If Have you been medically prescribed any of the following to assist with the management of your neu... = 15. I have not been medically prescribed anything for my neurological symptoms

Q4.4 On average, how do your neurological symptoms feel after taking your medication?
1- Symptom not noticeable
2- Symptom barely noticeable
3- Symptom somewhat noticeable
4- Symptom somewhat dulled
5- No change in symptom

	0	1	2	3	4	5
On average, how do your neurological symptoms feel after taking your medication? ()						

Carry Forward Selected Choices - Entered Text from "Have you been medically prescribed any of the following to assist with the management of your neurological symptoms?"

Q4.5 How long have you been using your medication?

1- Less than 1 month
2- 1-3 months
3- 3-5 months
4- 6-12 months
5- 1-2 years
6- 2 years plus

0	1	2	3	4	5	6

1. Amitriptyline/Endep ()	
2. Benzodiazepine ()	
3. Cannabidiol/CBD oil ()	
4. Duloxetine/Cymblta ()	
5. Fluoxetine/Prozac ()	
6. Lexapro ()	
7. Medicinal cannabis ()	
8. Milnacipran/Ixel ()	
9. Palmitoylethanolamide/PEA ()	
10. Physical exercise ()	
11. Pregabalin/Lyrica ()	
12. Valium/Diazapam ()	
13. Zoloft/Sertraline ()	
14. Add your own ()	
15. I have not been medically prescribed anything for my neurological symptoms ()	

End of Block: Neurological symptoms

Start of Block: Muscle and joint symptoms

Q5.1 Please select your symptoms of fibromyalgia associated with your muscles and joints (you can select more than one).

- [ ] 1. Swelling in joints and limbs (1)
- [ ] 2. Muscle tightness and stiffness (2)
- [ ] 3. Muscle weakness (4)
- [ ] 4. Muscle numbness/tingling/spasms (3)
- [ ] 5. Add your own (5) _____
- [ ] 6. None (6)

Skip To: End of Block If Please select your symptoms of fibromyalgia associated with your muscles and joints (you can sele... = 6. None

Q5.2 How frequent are your symptoms associated with your muscles and joints?

1- Less than 1 day each month
2- 1-2 days out of the month
3- 3-4 days out of the month
4- 1-2 days out of 7
5- 3-4 days out of 7
6- 5-6 days out of 7
7- Daily, mostly in the evenings
8- Daily, mostly in the morning

	0 1 2 3 4 5 6 7 8
How frequent are your symptoms associated with your muscles and joints? ()	

Q5.3 Have you been medically prescribed any of the following to assist with the management of your muscular and joint symptoms?

- [ ] 1. Cannabidiol/ CBD oil (1)
- [ ] 2. Duloxetine/Cymbalta (2)
- [ ] 3. Medicinal cannabis (3)
- [ ] 4. Palmitoylethanolamide/PEA (4)
- [ ] 5. Physical exercise (5)
- [ ] 6. Pregabalin/Lyrica (6)
- [ ] 7. Add your own (7) _____
- [ ] 8. I have not been medically prescribed anything for my muscular symptoms (8)

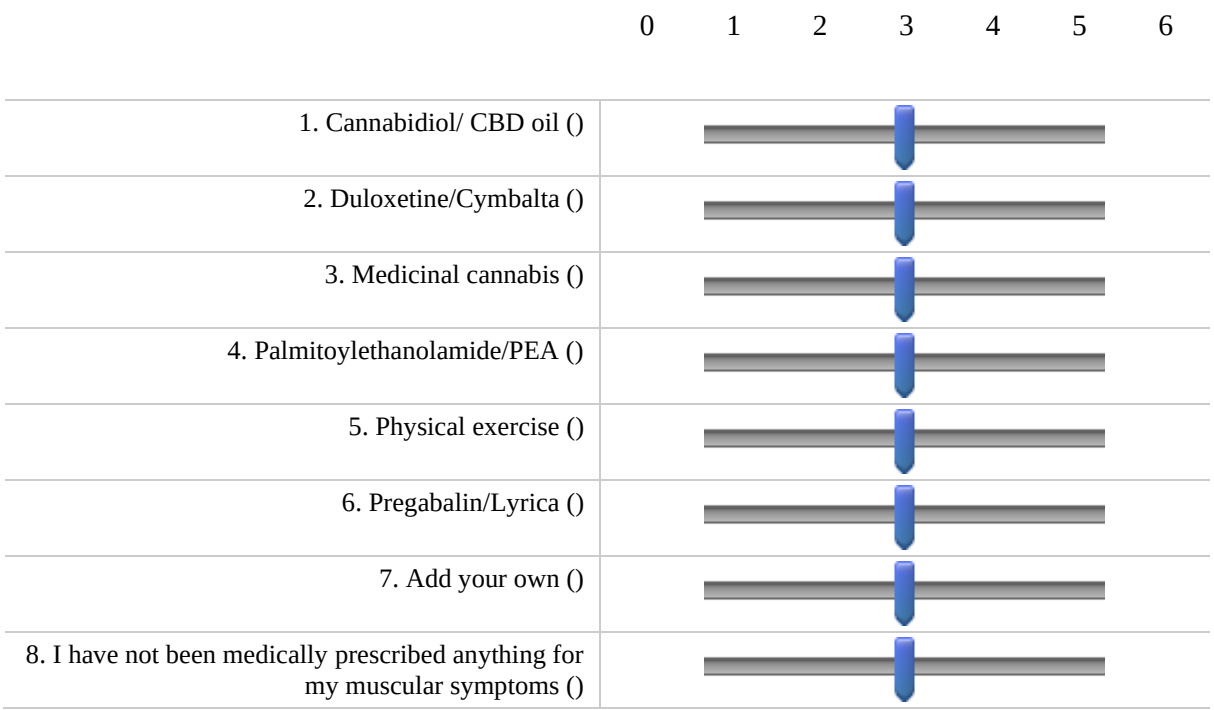
Skip To: End of Block If Have you been medically prescribed any of the following to assist with the management of your mus... = 8. I have not been medically prescribed anything for my muscular symptoms

Q5.4 On average, how do your muscle and joint symptoms feel after taking your medication?
1- No change in symptom
2- Symptom somewhat dulled
3- Symptom somewhat noticeable
4- Symptom barely noticeable
5- Symptom not noticeable

	0 1 2 3 4 5
On average, how do your muscle and joint symptoms feel after taking your medication? ()	

Carry Forward Selected Choices - Entered Text from "Have you been medically prescribed any of the following to assist with the management of your muscular and joint symptoms? "

Q5.5 How long have you been using this medication?
1- Less than 1 month
2- 1-3 months
3- 3-5 months
4- 6-12 months
5- 1-2 years
6- 2 years plus



End of Block: Muscle and joint symptoms

Start of Block: Symptoms other

Q6.1 Have you been diagnosed with other disease/s?

- 1. Yes (1)
- 2. No (2)

Skip To: Q6.2 If Have you been diagnosed with other disease/s? = 1. Yes
Skip To: Q6.3 If Have you been diagnosed with other disease/s? = 2. No

Q6.2 What disease/condition have you been medically diagnosed with? (you may select more than one)

- 1. Cancer (15)
- 2. Type 1 diabetes mellitus (13)
- 3. Type 2 diabetes mellitus (19)
- 4. High cholesterol (14)
- 5. Lupus (8)
- 6. Obesity (11)
- 7. Osteoarthritis (6)
- 8. Post-traumatic stress disorder (PTSD) (9)
- 9. Rheumatoid arthritis (7)
- 10. Add your own (10) _____

Q6.3 Do you/ have you ever claimed under the National Disability Insurance Scheme (NDIS) for fibromyalgia?

- ○ 1. Yes (1)
- ○ 2. No (2)

End of Block: Symptoms other

Start of Block: Alternative therapies

Q7.1 In this section we will be asking questions about therapies you use that are not prescribed by a medical professional. Depending on where you live this may include the use of illegally obtained cannabis. Remember, this survey is de-identified, the information collected in this survey is not linked to you or your personal information.

Have you/do you use any of the below alternate therapies for your symptoms of fibromyalgia?

- [ ] 1. 5-HTP (amino acid 5-Hydroxytryptophan) (1)
- [ ] 2. Cannabis plant (2)
- [ ] 3. CBD oil (3)
- [ ] 4. Coenzyme Q10 (4)
- [ ] 5. Hemp seed oil/Hemp seed oil products (5)
- [ ] 6. Magnesium (6)
- [ ] 7. Melatonin (7)
- [ ] 8. MSM (Methyl-sulfonyl-methane) (8)
- [ ] 9. Pro/prebiotics (9)
- [ ] 10. Turmeric (13)
- [ ] 11. Vitamin B (10)
- [ ] 12. Vitamin D (11)
- [ ] 13. None (14)
- [ ] 14. Add your own alternate therapy (15) _____

Skip To: End of Block If In this section we will be asking questions about therapies you use that are not prescribed by a... = 13. None

Display This Question:

If In this section we will be asking questions about therapies you use that are not prescribed by a... = 2. Cannabis plant

Q7.2 What category of symptom does the cannabis plant ease for you?

- [ ] 1. Pain symptoms (widespread pain, muscle aches,etc) (4)
- [ ] 2. Neurological symptoms (headache/memory,etc) (5)
- [ ] 3. Muscle and joint symptoms (swelling,numbness/tingling/spasms,etc) (6)
- [ ] 4. Add your own (7) _____

Display This Question

If In this section we will be asking questions about therapies you use that are not prescribed by a... = 2. Cannabis plant

Q7.3 How long have you been using the cannabis plant?

1- Less than 1 month
2- 1-3 months
3- 3-5 months
4- 6-12 months
5- 1-2 years
6- 2 years plus

	0	1	2	3	4	5	6
Cannabis ()							

Display This Question:

If What category of symptom does the cannabis plant ease for you? = 1. Pain symptoms (widespread pain, muscle aches,etc)

Q7.4 On average, how does your pain feel after using cannabis?
1- No pain
2- Unnoticeable pain
3- Low level mild pain
4- Moderate pain, I am aware of it but I can continue my day
5- Distracting pain, I am fully aware of my pain all day
6- Distressing pain, I give up on activities because of my pain
7- Unmanageable, I am aware of my pain and I cannot do most of my activities
8- Intense pain, my pain is so severe I cannot think of anything else, talking and listening are difficult

9- Severe pain, my pain is so severe I can barely talk or move
10- Unable to move, I need someone to assist me

	0 1 2 3 4 5 6 7 8 9 10
Cannabis ()	

End of Block: Alternative therapies

Start of Block: Overall satisfaction of treatment regime

Q8.1 Taking all your medications/therapy (medically prescribed or self-administered) into account, how satisfied are you with your current treatment regime?

1- Dissatisfied
2- Somewhat dissatisfied
3- Neutral
4- Somewhat satisfied
5- Satisfied

	0 1 2 3 4 5
How satisfied are you with your current therapy regime? ()	

Q8.2 Where do you learn about or search for alternate therapies to help in your management of fibromyalgia?

- [ ] 1. Google (1)
- [ ] 2. Social media (2)
- [ ] 3. My GP (3)
- [ ] 4. Friends/family (4)
- [ ] 5. None (6)
- [ ] 6. Add your own (5) _____

End of Block: Overall satisfaction of treatment regime

Start of Block: Dietary Fats

Q9.1 Now some questions relating to your diet. Which fats/oils do you consume in your diet?

- [ ] 1. Almond oil/butter (11)
- [ ] 2. Avocado oil (7)
- [ ] 3. Butter (animal) (5)
- [ ] 4. Canola oil (3)
- [ ] 5. Coconut oil (12)
- [ ] 6. Flaxseed oil (16)
- [ ] 7. Fish oil (17)
- [ ] 8. Ghee (9)
- [ ] 9. Margarine (10)
- [ ] 10. Nuttelex (8)
- [ ] 11. Extra virgin olive oil (6)
- [ ] 12. Peanut oil (2)
- [ ] 13. Sunflower oil (4)
- [ ] 14. Walnut oil (18)
- [ ] 15. None (13)
- [ ] 16. Add your own (15) _____

Skip To: End of Block If Now some questions relating to your diet. Which fats/oils do you consume in your diet? = 15. None

Carry Forward Selected Choices - Entered Text from "Now some questions relating to your diet. Which fats/oils do you consume in your diet?"

Q9.2 On average, within 14 days, how many times would you consume the fats/oils in your diet?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

1. Almond oil/butter ()	
2. Avocado oil ()	
3. Butter (animal) ()	
4. Canola oil ()	
5. Coconut oil ()	
6. Flaxseed oil ()	
7. Fish oil ()	
8. Ghee ()	
9. Margarine ()	
10. Nuttelex ()	
11. Extra virgin olive oil ()	
12. Peanut oil ()	
13. Sunflower oil ()	
14. Walnut oil ()	
15. None ()	
16. Add your own ()	

Carry Forward Selected Choices - Entered Text from "Now some questions relating to your diet. Which fats/oils do you consume in your diet?"

Q9.3 On the days you consume the fat/oils, what quantity do you use in one serving?

1. Almond oil/butter (x11)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
2. Avocado oil (x7)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
3. Butter (animal) (x5)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
4. Canola oil (x3)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
5. Coconut oil (x12)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
6. Flaxseed oil (x16)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
7. Fish oil (x17)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
8. Ghee (x9)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
9. Margarine (x10)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
10. Nuttelex (x8)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
11. Extra virgin olive oil (x6)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
12. Peanut oil (x2)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
13. Sunflower oil (x4)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
14. Walnut oil (x18)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
15. None (x13)	▼ 1/2 tsp (2) ... 3 tbsp + (13)
16. Add your own (x15)	▼ 1/2 tsp (2) ... 3 tbsp + (13)

End of Block: Dietary Fats

Start of Block: General diet

Q10.1 On average, how many serves of vegetables do you usually eat each day?

An example of a "serve‟ of vegetables is 1/2 cup cooked green or orange vegetables, 1 cup leafy

green vegetables,1/2 medium potato, 1 tomato.

- ○ 1. I do not eat vegetables (9)
- ○ 2. less than 1 serve a day (15)
- ○ 3. 1-2 serves a day (10)
- ○ 4. 2-3 serves a day (11)
- ○ 5. 3-4 serves a day (12)
- ○ 6. 4-5 serves a day (13)
- ○ 7. 5 serves or more (14)
- ○ 8. Don't know (8)
- ○ 9. Add your own (1) _____

Q10.2 On average, how many serves of fruit do you usually eat each day?
An example of a "serve" of fruit is 1 medium banana, apple, or pear, or 2 small plums, kiwi, or apricots, 1 cup of diced fruit, 1/2 cup fruit juice or 30 grams dried fruit.

- ○ 1. I do not eat fruit (9)
- ○ 2. less than 1/2 serve a day (15)
- ○ 3. 1/2-1 serve a day (10)
- ○ 4. 1-2 serves a day (11)
- ○ 5. 2-3 serves a day (12)
- ○ 6. 3 serves or more (14)
- ○ 7. Don't know (8)
- ○ 8. Add your own (1) _____

Q10.3 On average, how many serves of grains, cereals, bread, and rice do you eat each day? An example of a "serve" of grains etc, is 1 slice of bread (40 grams), one medium bread roll, 1/4 cup muesli or 1/2 cup of rice.

- ○ 1. I do not eat cereals or bread (9)
- ○ 2. less than 1 a serve a day (15)
- ○ 3. 1-2 serves a day (10)
- ○ 4. 2-3 serves a day (11)
- ○ 5. 3-4 serves a day (12)
- ○ 6. 4-5 serves a day (13)
- ○ 7. 5-6 serves a day (16)
- ○ 8. 6-7 serves a day (17)
- ○ 9. 7 serves or more (14)
- ○ 10. Don't know (8)
- ○ 11. Add your own (1) _____

Q10.4 On average, how many serves of lean meat, poultry, eggs, nuts and seeds, fish or legumes/beans do you eat each day?
An example of a "serve" of lean meats etc, is 65 grams lean meat, 80 grams cooked chicken, 100 grams cooked fish, 2 large eggs, 1 cup cooked lentils, and 30 grams of nuts and seeds.

- ○ 1. I do not eat lean meat, eggs, nuts, seeds, fish, or beans (9)
- ○ 2. less than 1/2 a serve a day (15)
- ○ 3. 1/2-1 serve a day (10)
- ○ 4. 1-2 serves a day (11)
- ○ 5. 2-3 serves a day (12)
- ○ 6. 3 serves or more (14)
- ○ 7. Don't know (8)
- ○ 8. Add your own (1) _____

Q10.5 On average how many serves of dairy products such as Milk, yoghurt, cheese, and milk alternatives do you consume each day?
An example of a "serve" of dairy is 1 cup of milk, 2 slices (40 grams) hard cheese, 1/2 cup ricotta cheese, 200 grams yoghurt, 1 cup of almond milk or rice milk.

- ○ 1. I do not eat dairy products (7)
- ○ 2. less than 1/2 a serve (1)
- ○ 3. 1/2 - 1 serve a day (2)
- ○ 4. 1-2 serves a day (3)
- ○ 5. 2-3 serves a day (4)
- ○ 6. 3 serves or more (5)
- ○ 7. Don't know (6)
- ○ 8. Add your own (8) _____

Q10.6 On average, how many serves of high fat or high sugar foods do you consume each day?
An example of a "serve" of high fat or sugar foods is 2 scoops of (full cream) ice cream, 2 slices of

salami or ham, 2-3 sweet biscuits, 1 can soft drink, 12 (60 grams) hot chips, 1 doughnut (40 grams) or 1 tbsp jam or honey.

- ○ 1. I do not eat high fat and high sugar foods (16)
- ○ 2. less than 1/2 a serve a day (15)
- ○ 3. 1/2- 1 serves a day (10)
- ○ 4. 1-2 serves a day (11)
- ○ 5. 2-3 serves a day (12)
- ○ 6. 3-4 serves a day (13)
- ○ 7. 4 serves or more (14)
- ○ 8. Don't know (8)
- ○ 9. Add your own (1) _____

Q10.7 Do you drink alcohol?

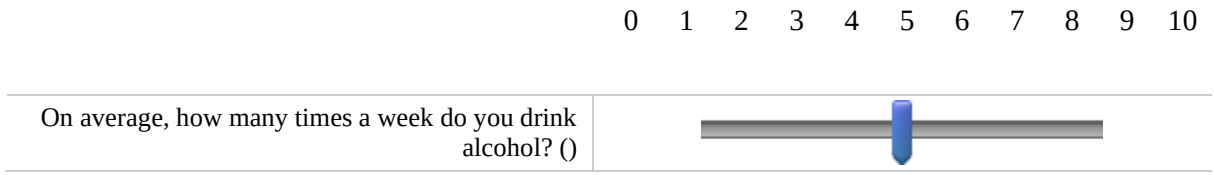
- ○ 1. Yes (1)
- ○ 2. No (2)

Skip To: Q10.6 If Do you drink alcohol? = 2. No

Q10.8 On average, how many times per week would you drink alcohol?

1- Less than 1 per fortnight
2- 1 per fortnight
3- Less than 1 per week
4- 1 per week
5- 1-2 per week

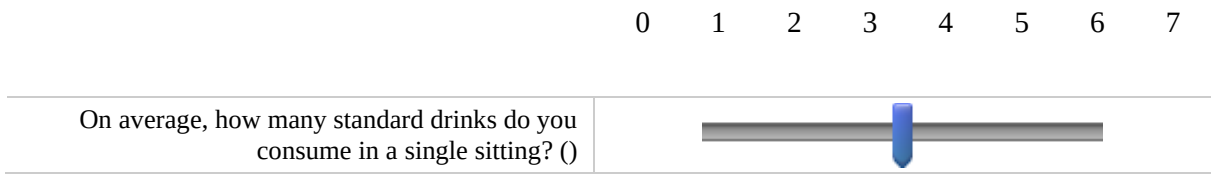
6- 3-4 per week
7- 5-6 per week
8- 7-8 per week
9- 9-10 per week
10- 10 plus per week



Q10.9 On average, how many standard serves of alcohol do you consume in a single sitting?

An example of a "standard serve" is 100ml wine, 285ml full strength beer, 60ml port/sherry or 30ml spirits.

1- 1-2 standard drinks
2- 3-4 standard drinks
3- 5-6 standard drinks
4- 6-7 standard drinks
5- 8-9 standard drinks
6- 9-10 standard drinks
7- more than 10 standard drinks



Q10.10 How much water/fluids do you drink each day? Including tea, coffee, milk, and juices.

- ○ 1. 1-2 glasses a day (~200-400mL) (1)
- ○ 2. 4 glasses a day (~400-800mL) (2)
- ○ 3. 1-2 litres a day (3)
- ○ 4. 2-3 litres a day (8)
- ○ 5. 3 litres + a day (4)
- ○ 6. None (5)
- ○ 7. Add your own (6) _____

End of Block: General diet

Start of Block: Diet Change

Q11.1 Have you tried changing your diet to manage your symptoms of fibromyalgia? (e.g., vegetarian, removed dairy products, removed alcohol, removed meat products, reducing fat intake, reducing sugar intake etc)

- ○ 1. Yes (1)
- ○ 2. No (2)

Skip To: End of Block If Have you tried changing your diet to manage your symptoms of fibromyalgia? (e.g. vegetarian, remo... = 2. No

Q11.2 What diet change have you used to manage your symptoms of fibromyalgia?

- [ ] 1. Low fat (1)
- [ ] 2. Low sugar (2)
- [ ] 3. No alcohol (3)
- [ ] 4. Vegetarian (4)
- [ ] 5. Paleo/ Carnivore diet (5)
- [ ] 6. Reduced red meat (6)
- [ ] 7. Atkins (7)
- [ ] 8. Whole food diet (8)
- [ ] 9. Gluten free (10)
- [ ] 10. Add your own (9) _____

Carry Forward Selected Choices from "What diet change have you used to manage your symptoms of fibromyalgia?"

Q11.3 Which diet changes did you find helped or did not help your symptoms?

	Helped my symptoms (1)	Did not help my symptoms (2)
1. Low fat (x1)	○	○
2. Low sugar (x2)	○	○
3. No alcohol (x3)	○	○
4. Vegetarian (x4)	○	○
5. Paleo/ Carnivore diet (x5)	○	○
6. Reduced red meat (x6)	○	○
7. Atkins (x7)	○	○
8. Whole food diet (x8)	○	○
9. Gluten free (x10)	○	○
10. Add your own (x9)	○	○

Q11.4 For those dietary changes that you found helped your symptoms, which symptoms did they help with? For example, headache/migraines, muscle aches and stiffness, widespread pain, fatigue, anxiety, and joint swelling etc.

_____

_____

Q11.5 How long did/have you maintained the diet change that helped your symptoms?

- ○ 1. less than 1 month, then stopped (6)
- ○ 2. 1-2 months, then stopped (5)
- ○ 3. 2-3 months, then stopped (7)
- ○ 4. Longer than 3 months, then stopped (8)
- ○ 5. 1 month or less and still on the diet (1)
- ○ 6. 1-3 months + and still on the diet (2)
- ○ 7. Over 3 months and still on the diet (3)
- ○ 8. Add your own (4) _____

Q11.6 For those dietary changes that you found did not help your symptoms, which symptoms were made worse? For example, headache/migraines, muscle aches and stiffness, widespread pain, fatigue, anxiety, and joint swelling etc.

_____

_____

Q11.7 How long did you maintained the diet change that made your symptoms worse?

- ○ 1. less than 1 month, then stopped (6)
- ○ 2. 1-2 months, then stopped (5)
- ○ 3. 2-3 months, then stopped (7)
- ○ 4. 3 months +, then stopped (8)
- ○ 5. Add your own (4) _____

End of Block: Diet Change

Start of Block: Exercise

Q12.1 You are doing so well, this is the final stage of the survey, we are nearly done. Do you exercise?

- 1. Yes (1)
- 2. No (2)
- 3. Sometimes (3)

Skip To: Q12.6 If You are doing so well, this is the final stage of the survey, we are nearly done. Do you exercise? = 2. No

Q12.2 What do you like to do for exercise? Choose as many as you like.

- [ ] 1. I take short walks (11)
- [ ] 2. I take long walks (1)
- [ ] 3. I go to the gym and use the machines (2)
- [ ] 4. I go to the gym and take exercise classes (3)
- [ ] 5. I go to the gym and use free weights (4)
- [ ] 6. I cycle (indoors and outdoors) (5)
- [ ] 7. I see a personal trainer and do a variety of exercises (6)
- [ ] 8. I do my exercise at home with weights (8)
- [ ] 9. I do my exercise at home with cardio equipment (12)
- [ ] 10. I jog/run (9)
- [ ] 11. I play and train for a competitive sport (10)
- [ ] 12. Add your own (7) _____

Carry Forward Selected Choices - Entered Text from "What do you like to do for exercise? Choose as many as you like."

Q12.3 On average, at what intensity do you prefer to exercise at?

1- Very light
2- Light, feels like I can exercise for hours
3- Somewhat light, can still talk while exercising
4- Moderately light, I breathe heavily and carry on a conversation
5- Moderate, I breathe heavily and find it difficult to carry on a conversation

6- Moderately vigorous, exercise is becoming uncomfortable but still able to speak
7- Vigorous, uncomfortable yet still able to speak
8- Hard, difficult to maintain intensity yet still able to speak
9- Very hard, difficult to maintain intensity and unable to speak
10- Maximal, cannot maintain intensity, must stop

	0 1 2 3 4 5 6 7 8 9 10
1. I take short walks ()	
2. I take long walks ()	
3. I go to the gym and use the machines ()	
4. I go to the gym and take exercise classes ()	
5. I go to the gym and use free weights ()	
6. I cycle (indoors and outdoors) ()	
7. I see a personal trainer and do a variety of exercises ()	
8. I do my exercise at home with weights ()	
9. I do my exercise at home with cardio equipment ()	
10. I jog/run ()	
11. I play and train for a competitive sport ()	
12. Add your own ()	

Q12.4 On average, how long do you like to exercise at this intensity?

1- 10-30 minutes a session
2- more than 30 minutes, less than 1 hour
3- 1.5 hours
4- 2 hours
5- 2 hours plus

0 1 2 3 4 5

On average, how long do you exercise for? ()	

Q12.5 On average, how many times in a week (7 days) do you exercise?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

On average, how many times a week do you exercise ()	

Q12.6

In the last 7 days, how many times have you walked continuously for at least 10 minutes? This could have been for recreation, exercise or to get to or from places.

0 2 4 7 9 11 13 15 18 20 22

I walked continuously for 10 minutes X times in the last week. ()	

End of Block: Exercise

Start of Block: End of survey

Q13.1 Thank you for taking the time to complete this survey. Your responses will add to the knowledge and ongoing research into fibromyalgia. The survey is now complete.

For some people answering questions about the symptoms they suffer with fibromyalgia and how effect their treatments are may cause distress. If you feel that you do need to talk to someone, please contact Beyond Blue on 1300 22 4636 or visit beyondblue.org.au or consult with your health professional.

One final question before you go. Are you interested in being a part of further research into fibromyalgia?

- ○ 1. Yes, I want to be a part of further research opportunities into fibromyalgia. (4)
- ○ 2. No, I am not interested in further research into fibromyalgia. (5)

Skip To: End of Survey If Thank you for taking the time to complete this survey. Your responses will add to the knowledge a... = 2. No, I am not interested in further research into fibromyalgia.

Q13.2 To express an interest in future studies into fibromyalgia please send you expression of interest HERE and our researchers will be in touch.

End of Block: End of survey